WATCHMAN Left Atrial Appendage Closure (LAAC) Technology for Patients with Non-valvular Atrial Fibrillation (AF)

October 8, 2014

Boston Scientific Corporation

FDA Circulatory System Devices Panel

Introduction to WATCHMAN LAAC Technology

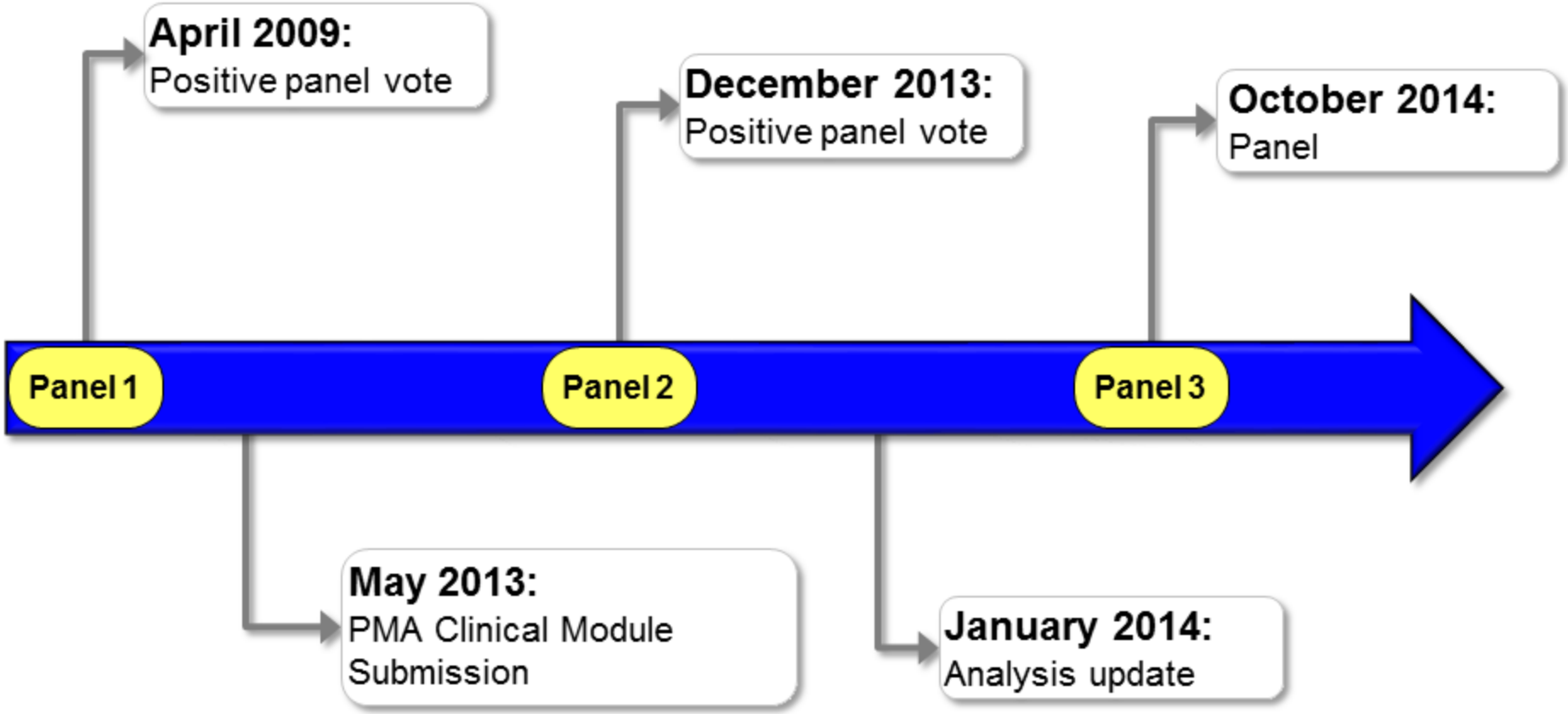
Kenneth Stein, MD

Chief Medical Officer

Rhythm Management

Boston Scientific Corporation

WATCHMAN US Regulatory History

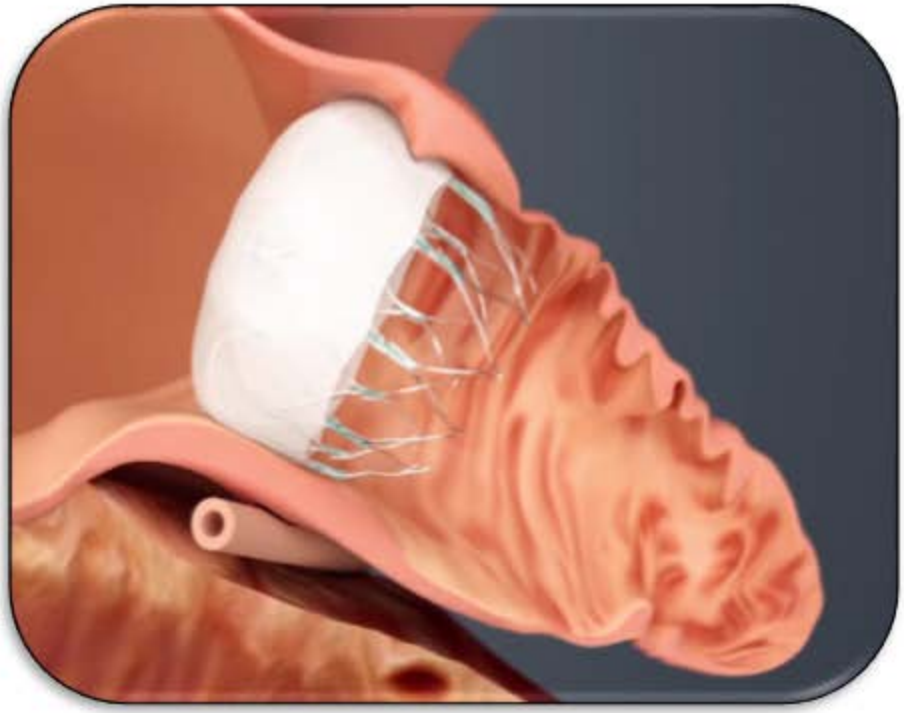


Why Are We Here Today?

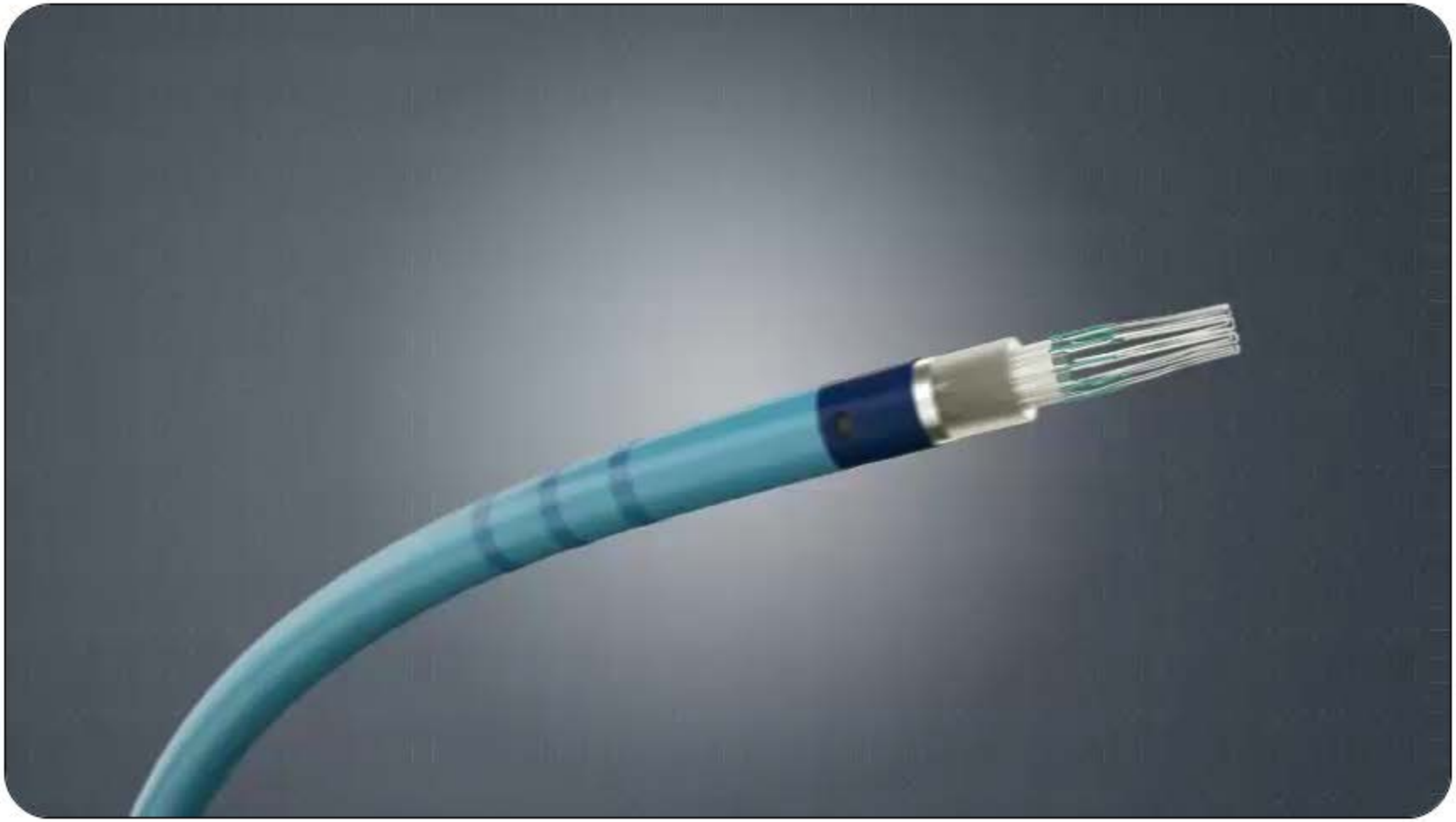
- Additional primary efficacy events* occurred in PREVAIL patients since PMA dataset was submitted
  - 2:1 Randomization
    - 10 new WATCHMAN events
    - 5 new warfarin events
- Perceived divergence between randomized groups in PREVAIL
- Consistency of device performance across trials

*composite of stroke, systemic embolism, or cardiovascular/unexplained death

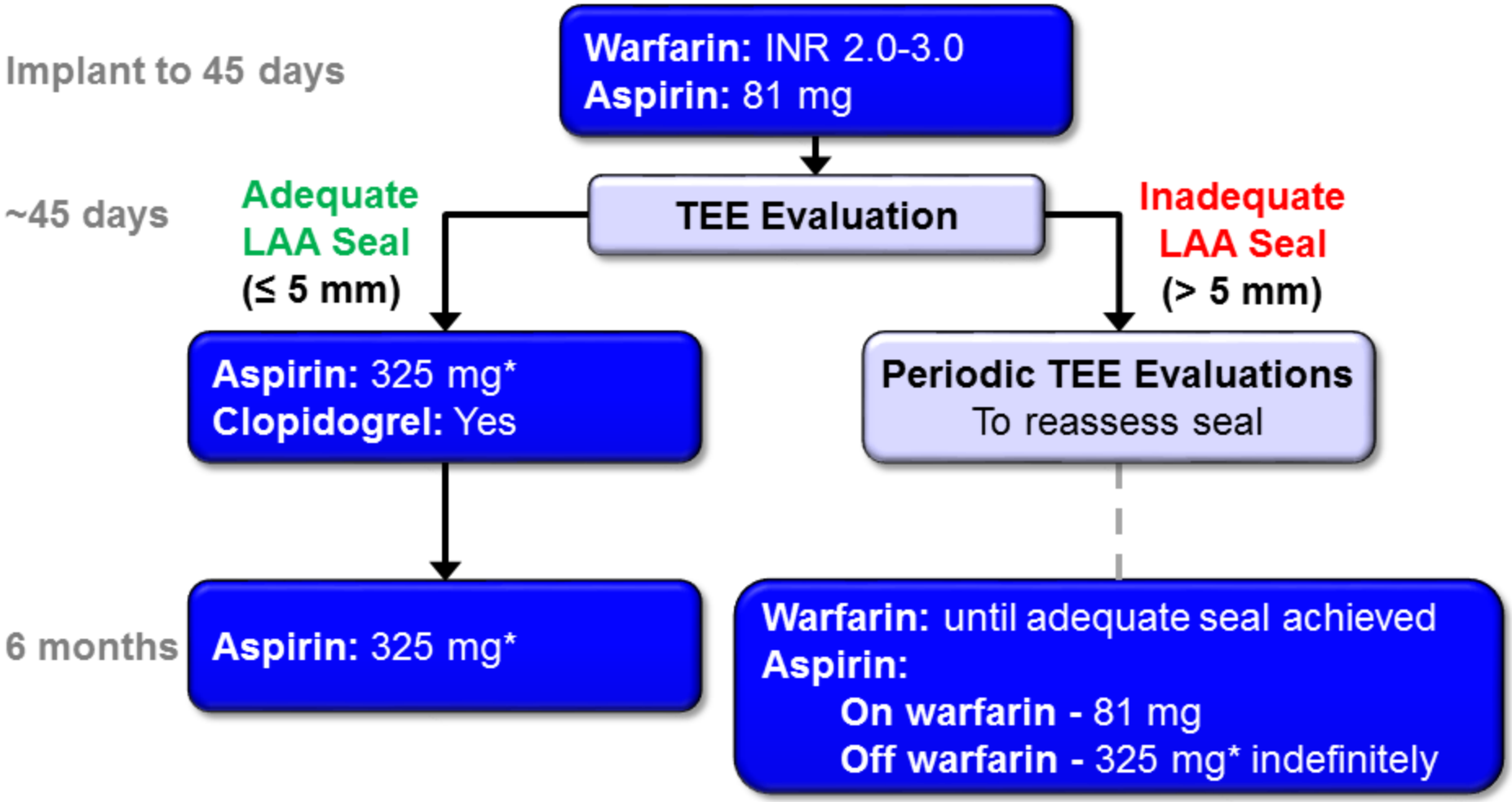
WATCHMAN Left Atrial Appendage Closure (LAAC)Technology



WATCHMAN Implant Procedure



Post-implant Management Includes TEE and Medication



*Recommended dosage

WATCHMAN Proposed Indication

The WATCHMAN LAAC Device is indicated to reduce the risk of thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism.

WATCHMAN Proposed Intended Use

The WATCHMAN LAAC Device is a percutaneous, transcatheter closure device intended for non-surgical closure of the left atrial appendage. In considering the use of the WATCHMAN LAAC Device, the benefits and risks of the device and the rationale for an alternative to chronic warfarin therapy should be taken into account.

WATCHMAN: A Safe and Effective Alternative Therapy

- NOT a broad first line replacement for oral anticoagulants
- IS an alternative for patients eligible for warfarin, with reasons to seek another long-term therapeutic option

WATCHMAN Totality of Data

- Procedural safety
- Efficacy in all studies
- Performance consistency
- Supplemental analyses

Agenda

Unmet Needs & Trial Design	**Shephal Doshi, MD** Electrophysiologist Pacific Heart Institute
Results	**Vivek Reddy, MD** Electrophysiologist Mount Sinai Medical Center
Post-approval Plan	**Kenneth Stein, MD** Chief Medical Officer, Rhythm Management Boston Scientific
Benefit-Risk and Conclusion	**Kenneth Huber, MD** Interventional Cardiologist Saint Luke's Mid America Heart Institute

Additional Experts

- **David Holmes, MD**
  Interventional Cardiologist
  Mayo Clinic

- **Stephen Hustead, DO**
  DSMB Chair
  Electrophysiologist
  Metropolitan Heart and Vascular Institute

- **Christopher Mullin, MS**
  Statistician
  NAMSA

- **Robert A. Taylor, MD**
  CEC
  Neurologist
  Stroke and Neurovascular Center of Central California

Unmet Need For Oral Anticoagulation Alternative

Shephal Doshi, MD

Electrophysiologist

Pacific Heart Institute

AF and Stroke Associated with Morbidity and Mortality

- AF increases the risk of stroke 4 - 5 times[1]
  - Higher risk: older patients and those with prior stroke or TIA[2]
  - AF is responsible for 15 - 20% of all strokes, particularly in older patients[3-4]
- AF results in greater disability compared to non-AF related stroke
  - Larger infarcts[5] and more severe hemorrhagic transformation[6]
  - High mortality[7] and stroke recurrence rate[8]

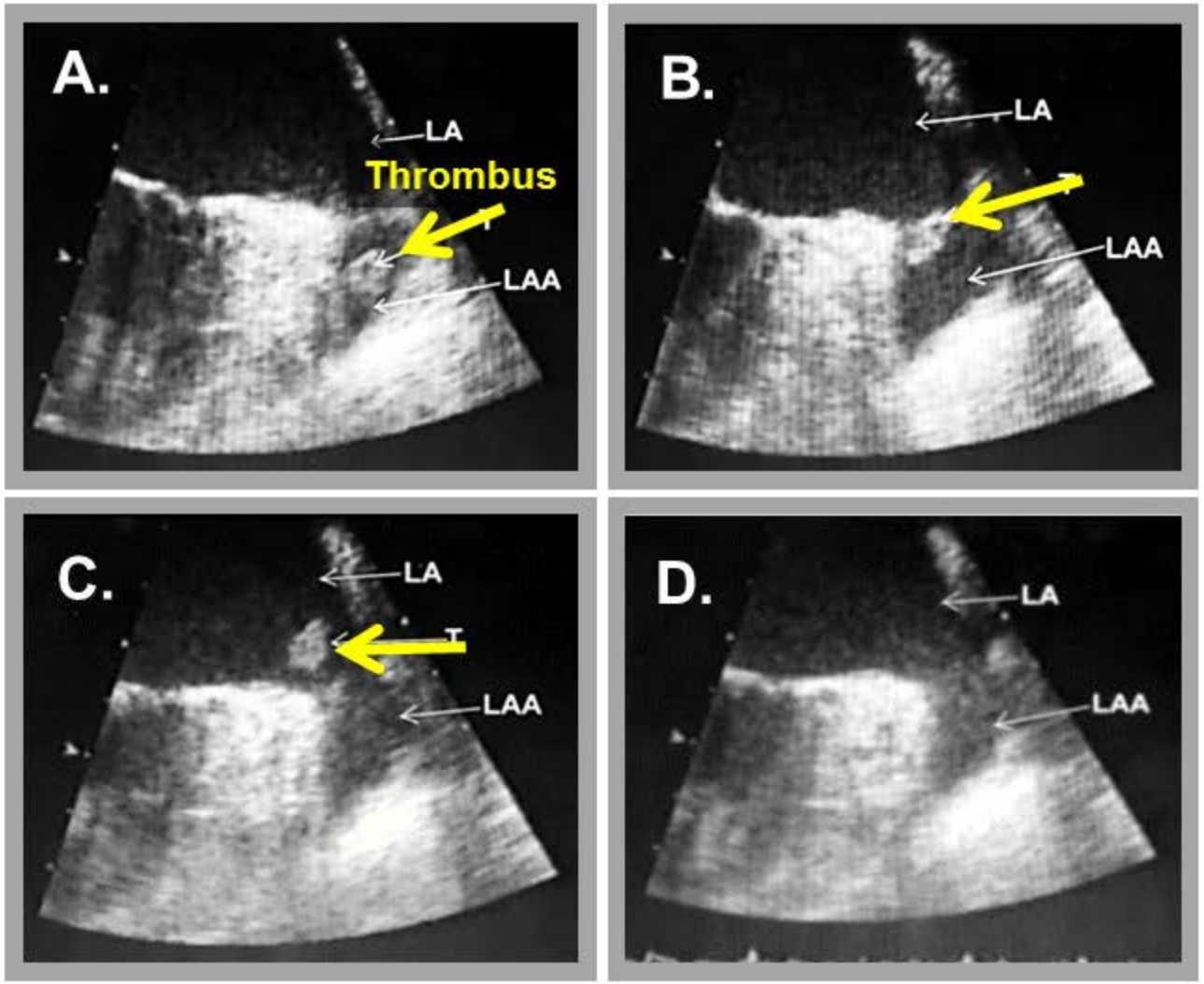
1. Wolf PA, Stroke (1991); 2. Gage BF, JAMA (2001); 3. Go AS, Am J Geriatr Cardiol (2005); 4. Hayes BD, Clin Geriatric Med (2007); 5. Jorgensen HS, Stroke (1996); 6. Tu HT, Int J Stroke (2013); 7. McGrath ER, Neurology (2013); 8. Penado S, Am J Med (2003)

AF Creates Environment for Thrombus Formation in LAA

- Stasis-related LA thrombus is a predictor of TIA[1] and ischemic stroke[2]
- In non-valvular AF, 90% of LA thrombus originate in the left atrial appendage[3]

1. Stoddard et al. Am Heart J. (2003); 2. Goldman et al. J Am Soc Echocardiogr (1999); 3. Blackshear & Odell. Cerebrovascular Disease (2000)

Development and Dislodgement of Thrombus Originating in the LAA



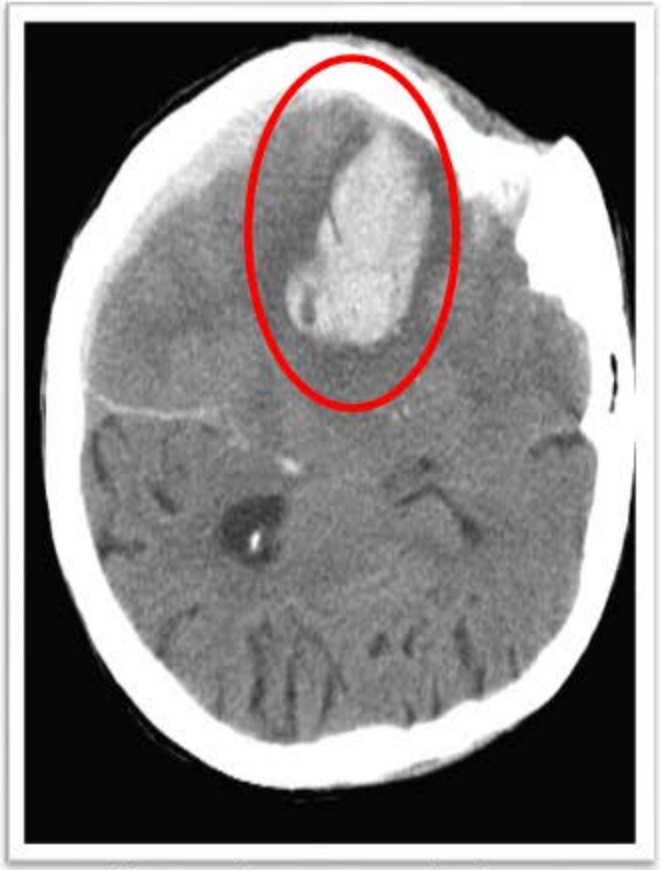
Parekh A et al. Circulation (2006)

2014 Treatment Guidelines to Prevent Strokes in Patients with AF

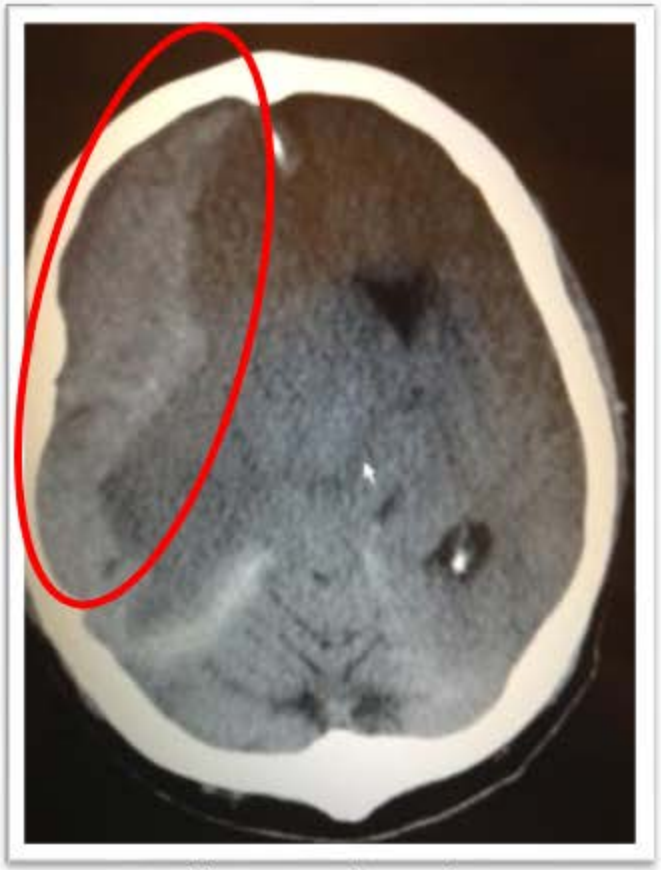
- Assess stroke risk
- Systemic anticoagulation
- CHA_2DS_2-VASc to characterize annual stroke risk
  - Score 1: Annual stroke risk 1.3%
  - Score ≥2: Annual stroke risk 2% to 24%
- CHA_2DS_2-VASc ≥1, consider warfarin, NOACs
- Balance benefit vs. bleeding risk

AHA/ACC/HRS Guidelines (2014)

Anticoagulant Therapy Carries Risk of Intracerebral Hemorrhage or Death



Spontaneous intra-parenchymal bleed



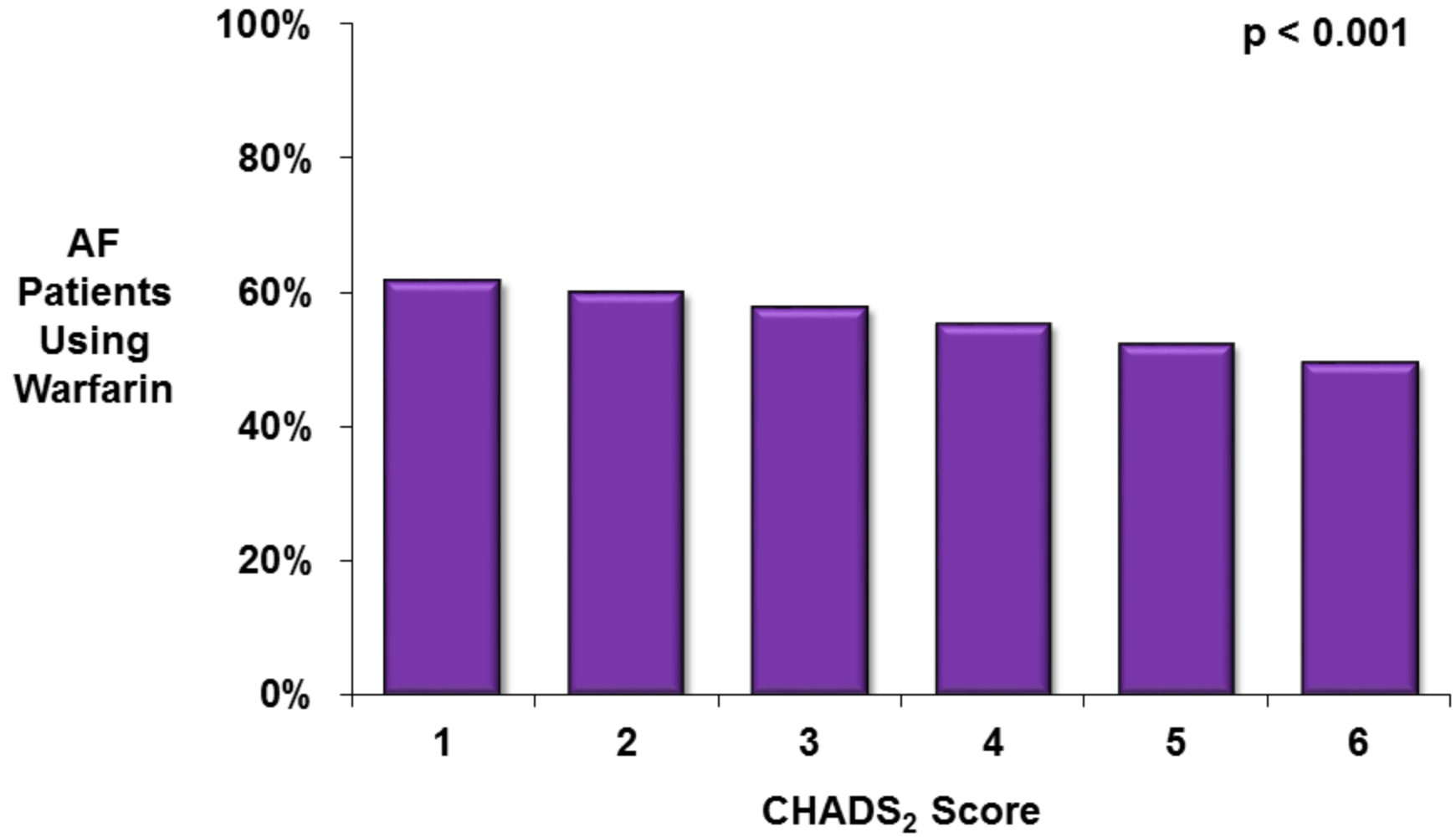
Hemorrhagic transformation

Physician Reasons for Warfarin Underuse in AF

- Most cited reasons
  - Bleeding risk and age
- Other factors influencing prescription:
  - Previous falls
  - Perceived fall risk
  - Comorbidities (cognitive impairment, alcohol)
  - Inability to comply with treatment

Age and Aging 2011; 40: 675–83

As Stroke Risk Increases, Warfarin Use Decreases



Piccini. Heart Rhythm (2012)

Discontinuation and Major Bleeding Rates with NOACs

Treatment	Study Drug Discontinuation Rate	Major Bleeding (rate/year)
Rivaroxaban[1]	24%	3.6%
Apixaban[2]	22%	2.1%
Dabigatran[3] (150 mg)	21%	3.3%
Warfarin[1-3]	17 – 28%	3.1 – 3.6%

1: Patel MR. N Engl J Med (2011); 2. Granger CB. N Engl J Med (2011); 3. Connolly SJ. N Engl J Med (2009 Corrected)

Need for Alternative Therapeutic Strategies

- Long-term anticoagulation underutilized
- AF-related stroke is major public health problem
- Approximately half of high-risk patients unprotected from stroke
- Need FDA-approved alternatives

Trial Design and Patient Characteristics

PROTECT AF, PREVAIL, CAP, and CAP2

Study Designs

	Randomized Studies		Non-Randomized Registries	
	PROTECT AF N=800	**PREVAIL** N=463	**CAP** N=566	**CAP2** N=579
Enrollment	2005-2008	2010-2012	2008-2010	2012-2014
Randomization to warfarin	2:1	2:1	---	---
Follow-up	45 days; 6, 9, and 12 months; Annual visits and semi-annual phone visits for 2-5 years			

Pre-specified Composite Efficacy Endpoint Identical in All Trials

- Pre-specified composite endpoint reflects intent of the device.
- To show clinical comparability to warfarin for:
  - All stroke
  - Systemic embolism
  - Cardiovascular/unexplained death

Differences from PROTECT AF: PREVAIL Enrolled Higher Risk Patients

- Inclusion criteria change for $CHADS_2$ score
- Exclusion of patients taking clopidogrel
- Endpoints separating procedure-related events from long-term efficacy
- Enrollment milestones for new sites/operators

Agreed Upon Bayesian Design and Pre-specified Analyses

- Portion of PROTECT AF used as informative prior in PREVAIL
  - Poolable
    - Same device, control, and outcome measure
- PREVAIL not powered to make definitive conclusions
- PREVAIL pre-specified analysis was presented in December 2013
  - All analyses presented today are post hoc

PROTECT AF and CAP: Largest Datasets to Evaluate Totality of Data

	PROTECT AF	PREVAIL	CAP Registry	CAP2 Registry	Totals
Enrollment	2005-2008	2010-2012	2008-2010	2012-2014	
Enrolled	800	461	566	579	2406
Randomized	707	407	---	---	1114
WATCHMAN: warfarin (2:1)	463 : 244	269 :138	566	579	1877: 382
Mean Follow-up (years)	4.0	2.2	3.7	0.58	N/A
Patient-years	2717	860	2022	332	5931

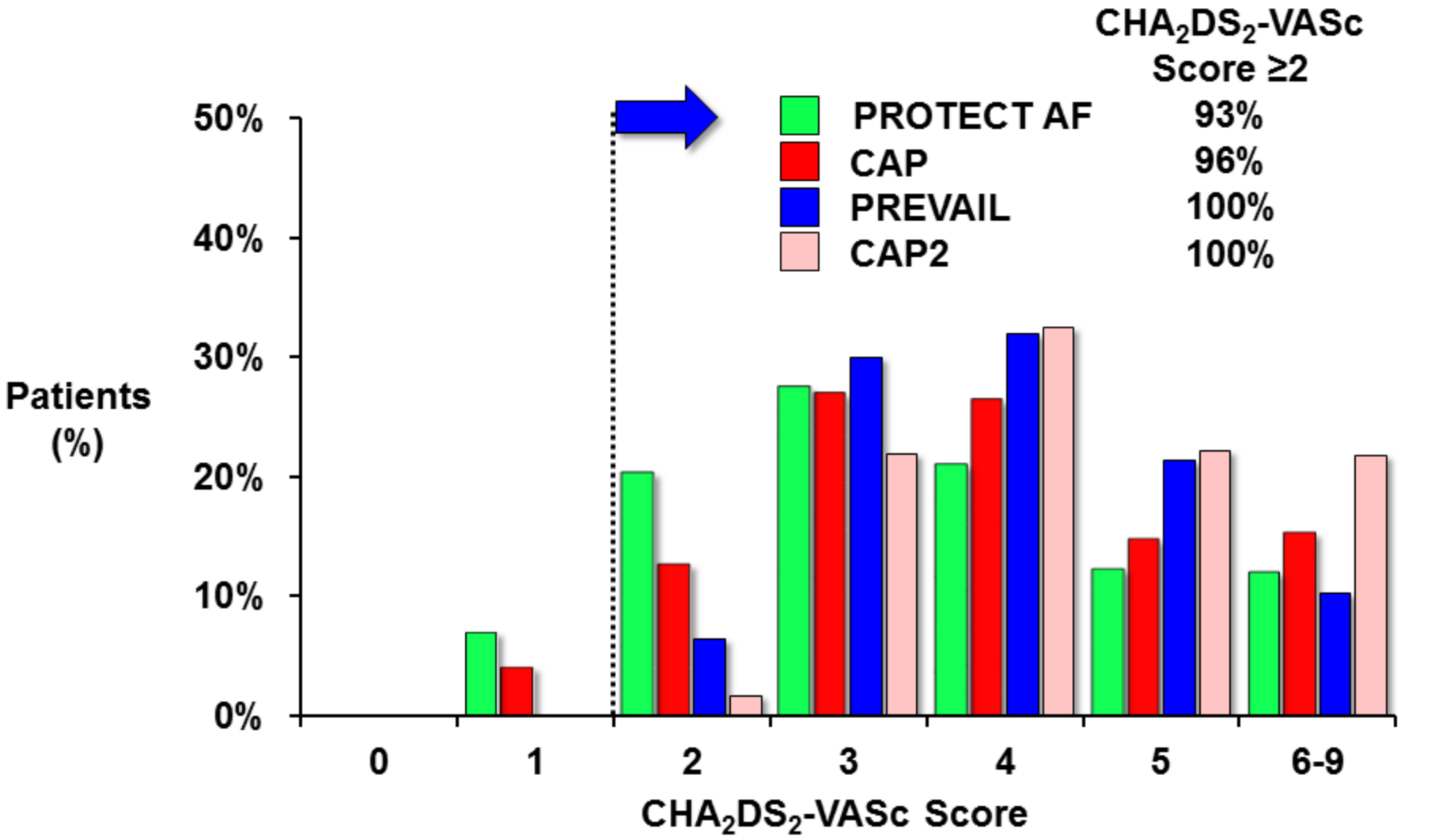
Patient Demographics Across Trials

Characteristic	PROTECT AF N=707	PREVAIL N=407	CAP N=566	CAP2 N=579
Age, mean ± SD	**72.0 ± 8.9**	**74.3 ± 7.4**	**74.0 ± 8.3**	**75.3 ± 8.0**
Sex (Male)	**70.3%**	**70.0%**	**65.5%**	**61.0%**
Ethnicity / Race				
Asian	**0.7%**	**0.5%**	**1.6%**	**0.7%**
Black/African American	**1.6%**	**1.7%**	**1.9%**	**1.2%**
Caucasian	**91.5%**	**94.4%**	**91.9%**	**94.1%**
Hispanic/Latino	**5.7%**	**2.7%**	**3.5%**	**2.1%**
Other	**0.6%**	**0.7%**	**1.1%**	**1.0%**

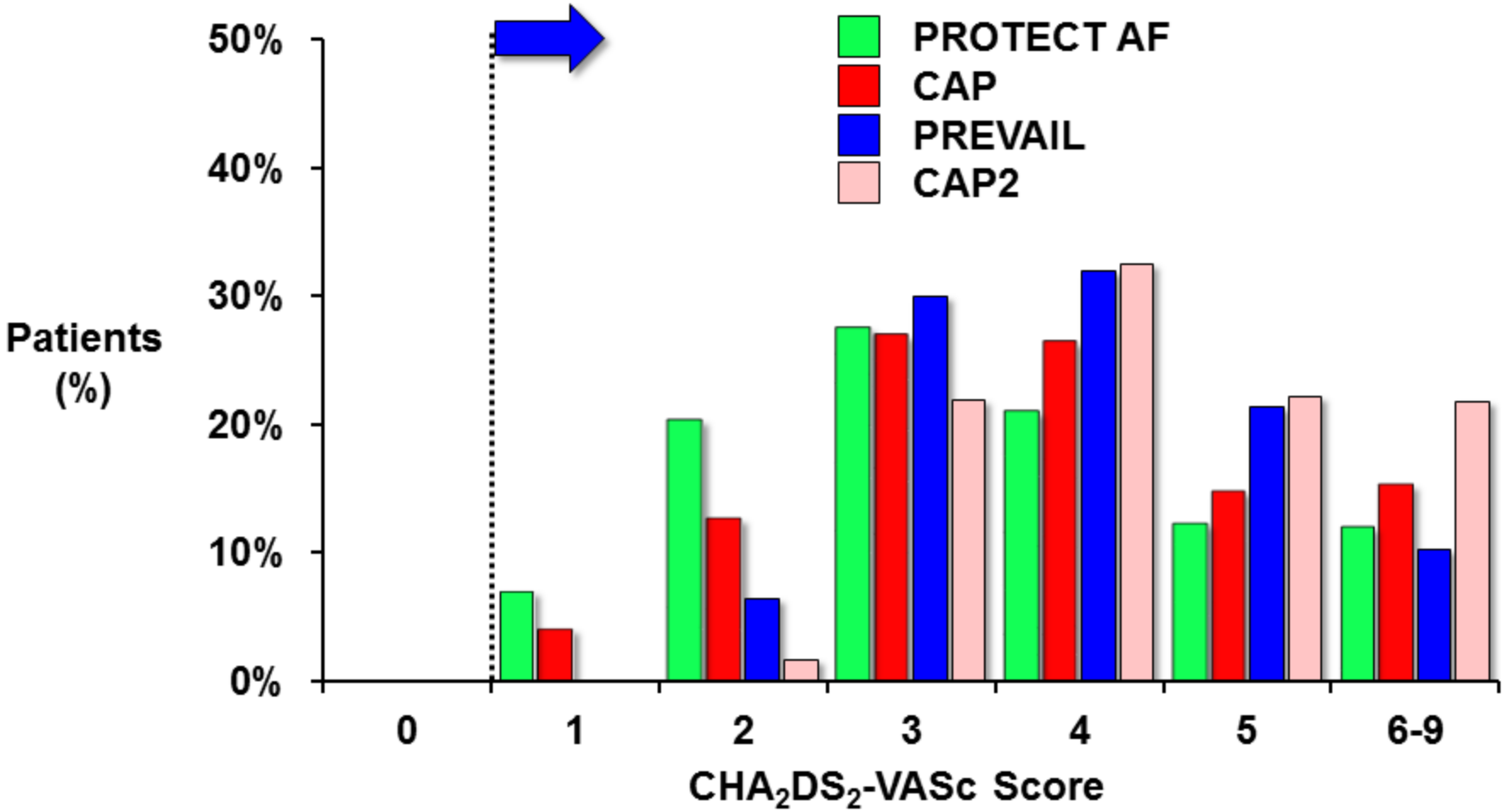
Patient Risk Factors Across Trials

Characteristic	PROTECT AF N=707	PREVAIL N=407	CAP N=566	CAP2 N=579	p-value
$CHADS_2$ Score	**2.2 ± 1.2**	**2.6 ± 1.0**	**2.4 ± 1.2**	**2.7 ± 1.1**	**<.0001**
$CHADS_2$ Risk Factors (% of Patients)					
CHF	26.9	19.1	23.3	27.1	0.004
Hypertension	89.8	88.8	91.4	92.5	0.15
Age ≥ 75	43.1	51.8	53.6	59.7	<0.001
Diabetes	26.2	24.9	32.4	33.7	0.001
Stroke/TIA	18.5	30.4	27.8	29.0	<0.0001
CHA_2DS_2-VASc	**3.5 ± 1.6**	**4.0 ± 1.2**	**3.9 ± 1.5**	**4.5 ± 1.3**	**<0.0001**

Majority of WATCHMAN Patients are High Risk



All WATCHMAN Patients Were Eligible for Warfarin



Over 90% Patients at Moderate to High Risk of Bleeding

Study	Patients (%) with HAS-BLED* Score		
	Low Risk (0)	Moderate Risk (1-2)	High Risk (3+)
PROTECT AF (N=707)	**6.4**	**73.7**	**19.9**
PREVAIL (N=407)	**1.7**	**68.6**	**29.7**
CAP (N=566)	**2.8**	**61.0**	**36.2**
CAP2 (N=579)	**2.8**	**69.9**	**28.3**
SPORTIF III/IV[1] (N=7329)	**24.0**	**61.0**	**15.0**

* Estimated

1. Lip, G. JACC 2011

Results

Vivek Reddy, MD

Electrophysiologist

Mount Sinai Medical Center

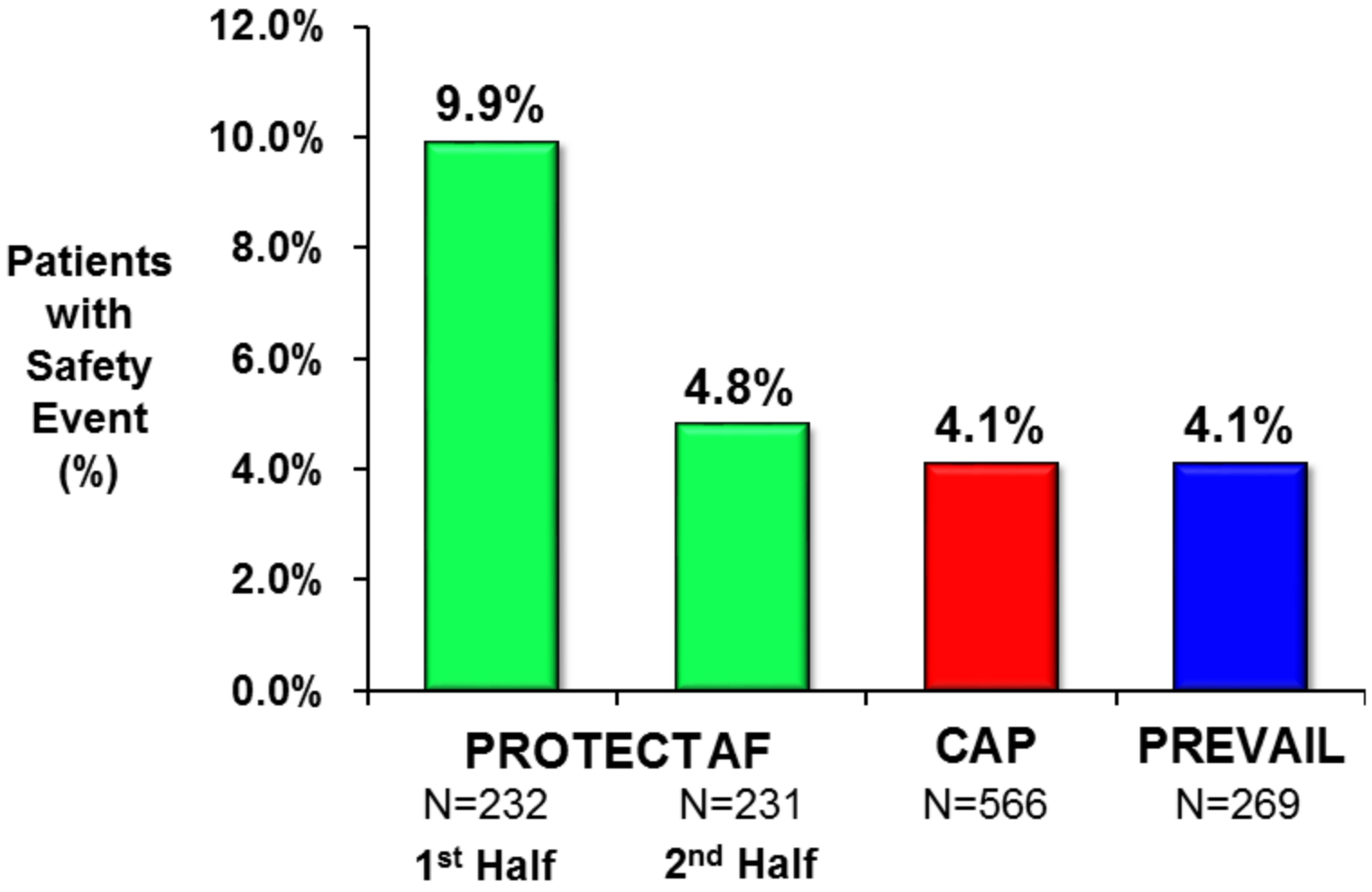
Clinical Results Agenda

- Procedural safety
- Efficacy in randomized studies
  - PROTECT AF
  - PREVAIL
- Performance consistency
- Totality of evidence

Totality of Data Support Watchman as Comparable Alternative to Warfarin

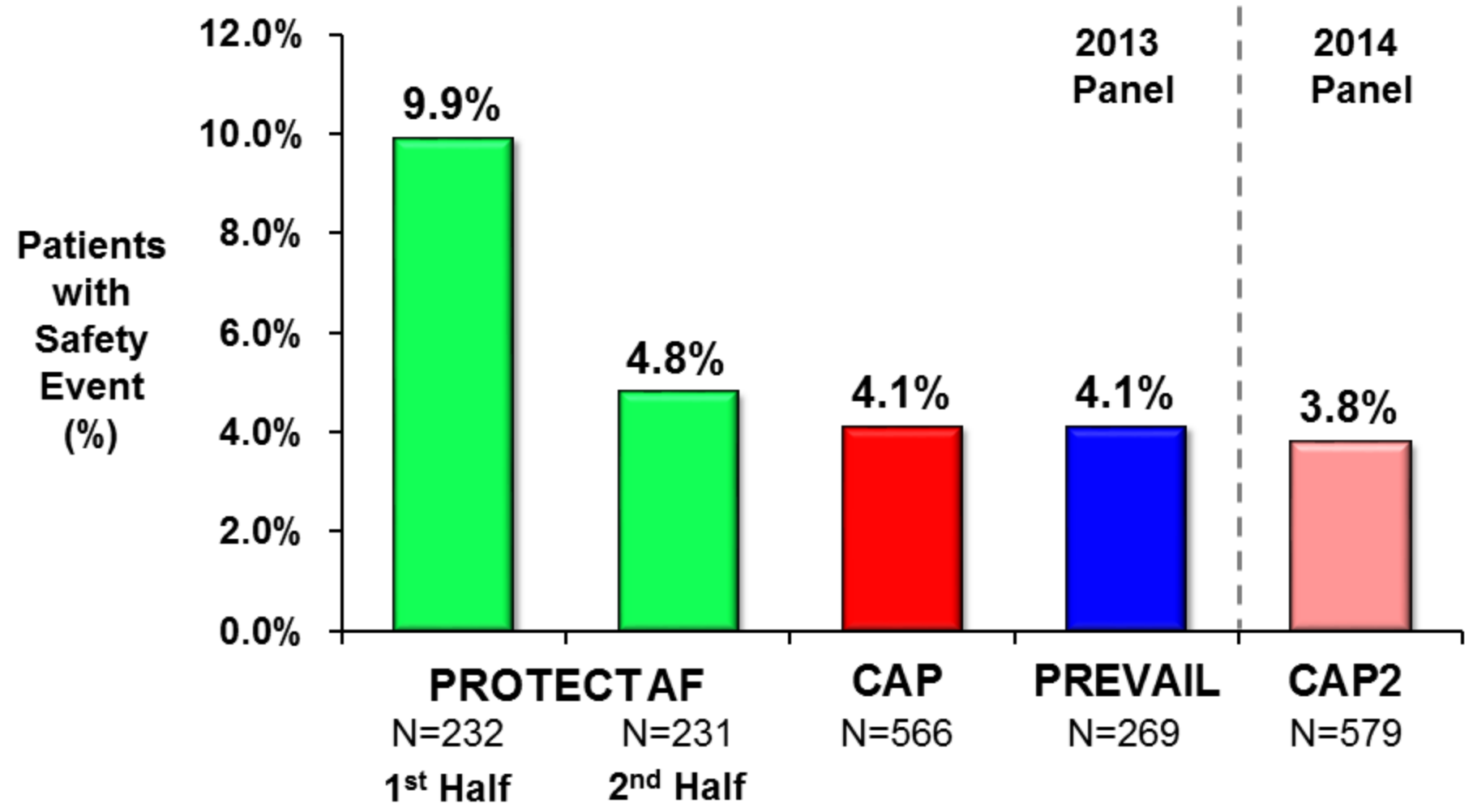
- Composite primary efficacy endpoint
  - All stroke
  - Systemic embolism
  - Cardiovascular/unexplained death
- Same composite endpoint in all trials
- Individual components were not primary endpoints
- Composite endpoint most fully assesses WATCHMAN efficacy

Favorable Procedural Safety Profile for 7-day Safety Events



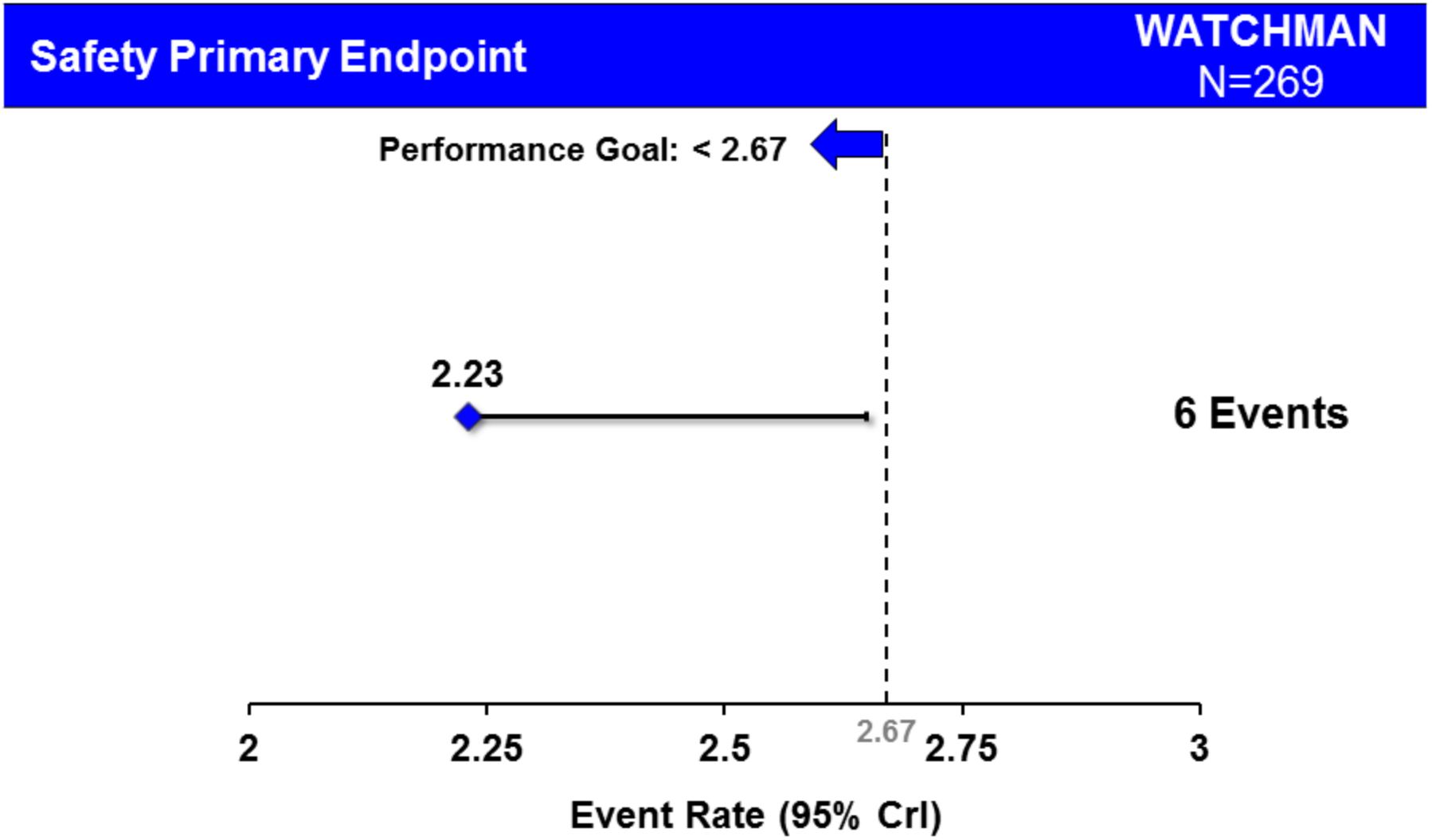
All Device and/or procedure-related serious adverse events within 7 Days

Favorable Procedural Safety Profile for 7-day Safety Events



All Device and/or procedure-related serious adverse events within 7 Days

PREVAIL Pre-specified Safety Primary Endpoint Met



Clinical Results Agenda

- Procedural safety
- Efficacy in randomized studies
  - PROTECT AF
  - PREVAIL
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PROTECT AF: Primary Efficacy Consistent and Superior to Warfarin

PROTECT AF	Rate Ratio	Posterior Probability	
		Non-inferiority	Superiority
2013 Panel (2621 Patient-years)			
Primary efficacy	**0.60**	**>99%**	**96%**
2014 Panel (2717 Patient-years)			
Primary efficacy	**0.61**	**>99%**	**95%**

PROTECT AF: Final Primary Efficacy Events Favor WATCHMAN

	Event Rate (per 100 Pt-Yrs)		Rate Ratio	Posterior Probability	
	WATCHMAN	Warfarin	(95% CrI)	Non-inferiority	Superiority
Primary efficacy	**2.2**	**3.7**	**0.61** (0.42, 1.07)	**>99.9%**	**95.4%**
Stroke (all)	**1.5**	**2.2**	**0.68** (0.42, 1.37)	**99.9%**	**83%**
Ischemic	**1.3**	**1.1**	**1.25** (0.72, 3.27)	**78%**	**15%**
Hemorrhagic	**0.2**	**1.1**	**0.15** (0.03, 0.49)	**>99.9%**	**99%**
Systemic embolism	**0.2**	**0.0**	**N/A**	**--**	**--**
Death (CV/unexplained)	**1.0**	**2.3**	**0.44** (0.26, 0.90)	**>99.9%**	**98.9%**

PROTECT AF: Disabling Stroke Favors WATCHMAN

- Disabling stroke defined as MRS change of 2 or more or cause of death related to stroke

PROTECT AF	Event Rate (per 100 pt-yrs) WATCHMAN N=463	Warfarin N=244	Hazard Ratio (95% CI)	p-value
Stroke (all)	**1.5**	**2.2**	**0.75** (0.42, 1.34)	**0.33**
Disabling	**0.4**	**1.3**	**0.33** (0.13, 0.85)	**0.02**
Non-disabling	**1.1**	**0.9**	**1.36** (0.59, 3.11)	**0.47**

Proportional Hazards Model

PROTECT AF: Final Primary Efficacy Events Favor WATCHMAN

	Event Rate (per 100 Pt-Yrs)		Rate Ratio	Posterior Probability	
	WATCHMAN	Warfarin	(95% CrI)	Non-inferiority	Superiority
Primary efficacy	**2.2**	**3.7**	**0.61** (0.42, 1.07)	**>99.9%**	**95.4%**
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Systemic embolism	**0.2**	**0.0**	**N/A**	**--**	**--**
Death (CV/unexplained)	**1.0**	**2.3**	**0.44** (0.26, 0.90)	**>99.9%**	**98.9%**

PROTECT AF: CV Mortality Favors WATCHMAN

Category	October 2014 Panel (2717 Patient Years) WATCHMAN N=463 %	Warfarin N=244 %	p-value
Cardiovascular	**3.9**	**9.0**	**0.009**
Unexplained/other	**1.0**	**2.0**	**0.33**
Sudden death	**0.9**	**1.6**	**0.46**
Heart failure	**0.9**	**0.8**	**1.00**
Hemorrhagic stroke	**0.4**	**3.3**	**0.004**
Myocardial infarction	**0.4**	**0.8**	**0.61**
Ischemic stroke	**0.2**	**0.4**	**1.00**

PROTECT AF: Patients in WATCHMAN Trials at Higher Risk of Bleeding

Study	Patients (%) with HAS-BLED* Score		
	Low Risk (0)	Moderate Risk (1-2)	High Risk (3+)
PROTECT AF (N=707)	**6.4**	**73.7**	**19.9**
PREVAIL (N=407)	**1.7**	**68.6**	**29.7**
CAP (N=566)	**2.8**	**61.0**	**36.2**
CAP2 (N=579)	**2.8**	**69.9**	**28.3**
SPORTIF III/IV[1] (N=7329)	**24.0**	**61**	**15**

* Estimated

1. Lip, G. JACC 2011

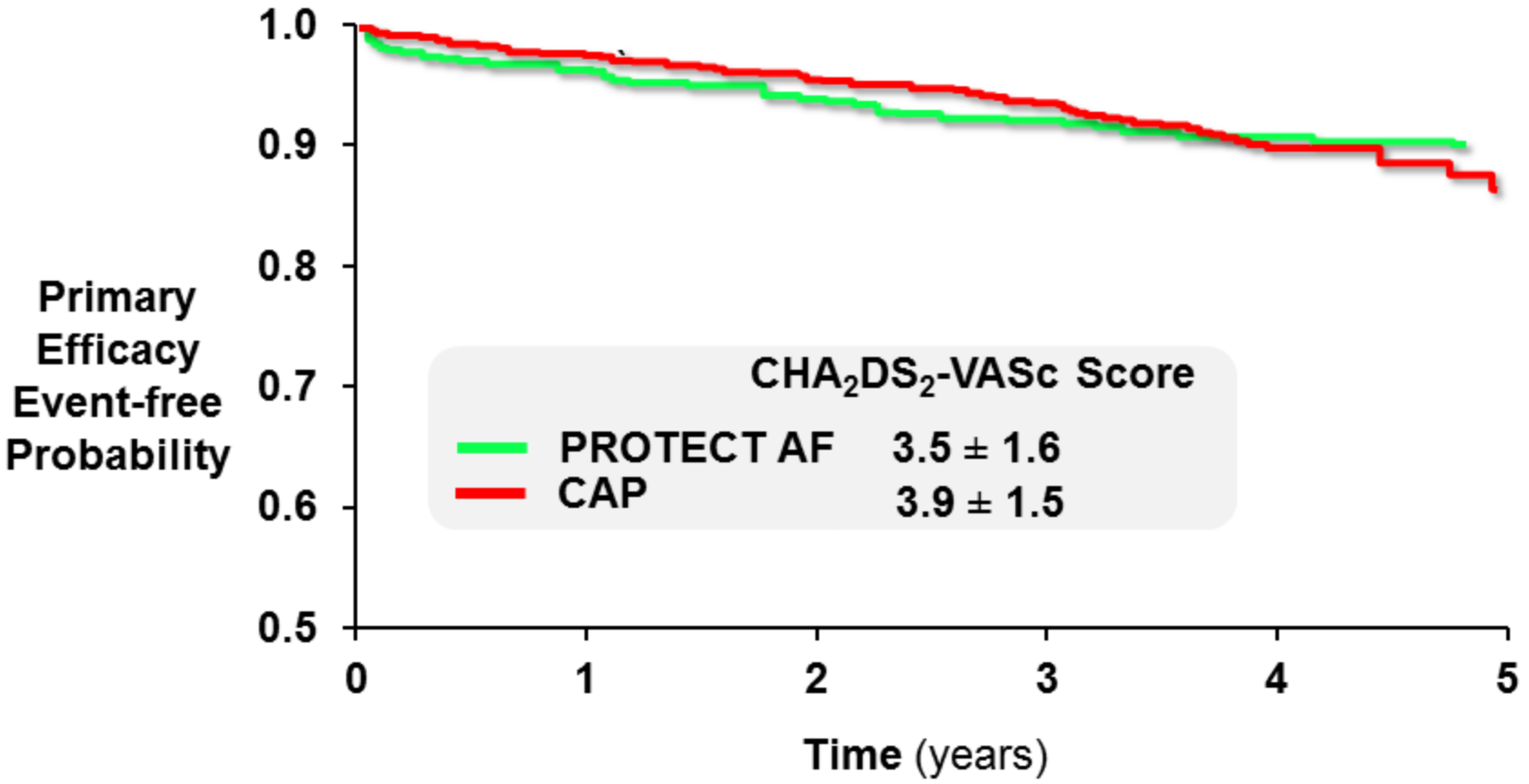
PROTECT AF: WATCHMAN Provides Hemorrhagic Stroke Reduction

- PROTECT AF hemorrhagic stroke rates
  - 1.1% in warfarin arm
  - 0.2% in WATCHMAN arm
  - 85% reduction with WATCHMAN
- Hypothetical hemorrhagic stroke rate
  - 0.5% in warfarin arm
  - Substantial reduction with WATCHMAN

PROTECT AF: Sensitivity Analysis Supports WATCHMAN Non-inferiority

	Rate (95% CrI)		Relative Risk (95% CrI)	Posterior Probabilities	
	WATCHMAN	Control		Non-inferiority	Superiority
Primary Analysis	**2.2** (1.7, 3.1)	**3.7** (2.4, 4.8)	**0.61** (0.42, 1.07)	**>99.9%**	**95.4%**
Disregard all control group patients with hemorrhagic stroke	**2.2** (1.7, 3.1)	**2.6** (1.5, 3.5)	**0.87** (0.59, 1.64)	**99.6%**	**54.9%**

CAP & PROTECT: Consistent Efficacy, No Signal of Increased Late Events



PROTECT AF	463	382	360	337	321	235
CAP	566	503	468	435	293	59

Clinical Results Agenda

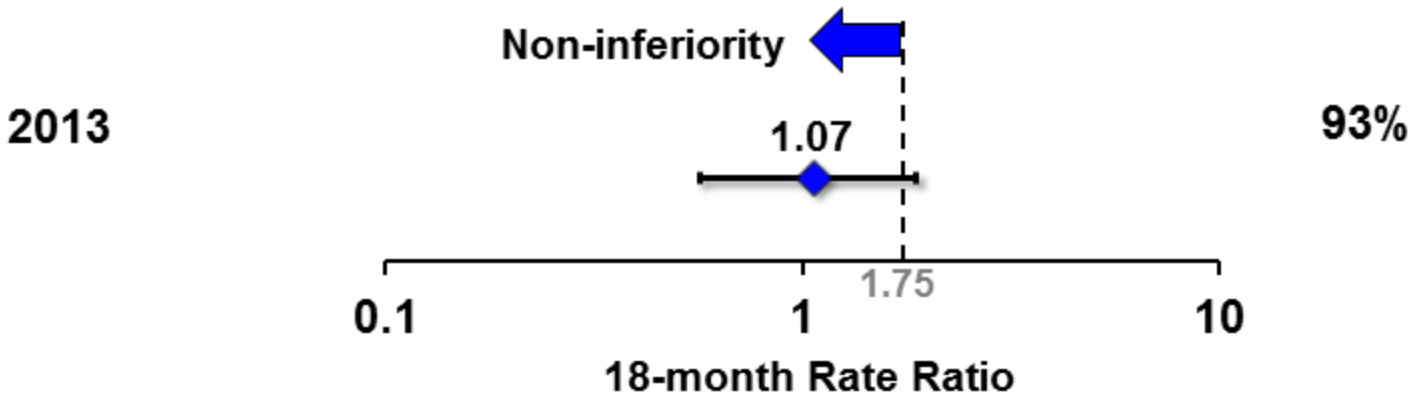
- Procedural safety
- Efficacy in randomized studies
  - PROTECT AF
  - PREVAIL
- Performance consistency
- Totality of evidence

PREVAIL: Pre-specified Analysis Presented at Panel 2013

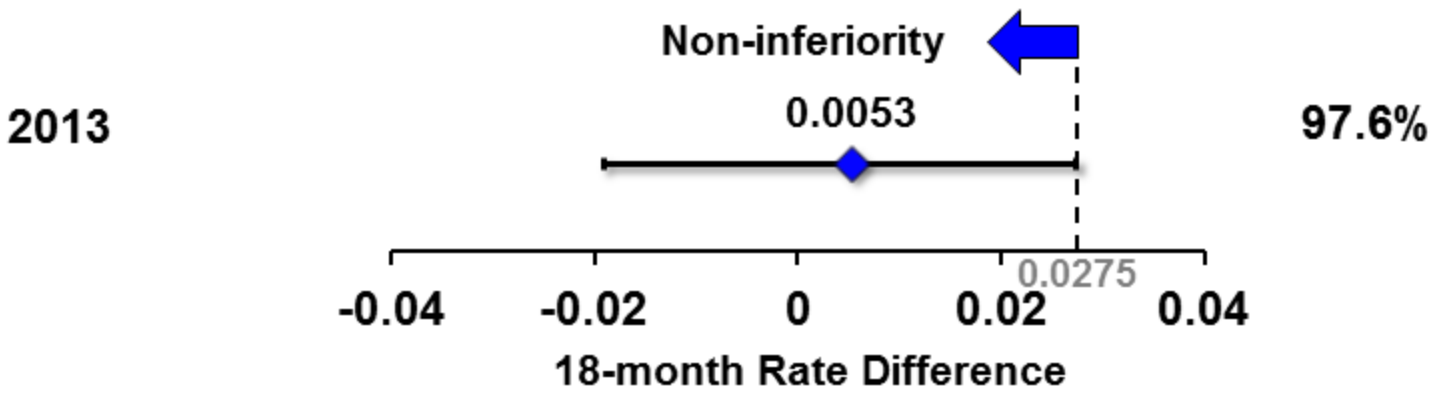
- All patients through 6 month of follow-up
- Primary efficacy endpoints
  - 1st Primary: stroke, SE, or CV/Unexplained death
  - 2nd Primary: ischemic stroke or SE (post 7 days)
- Modeled 18-month event rate based on piecewise exponential analysis with PROTECT AF as the informative prior

PREVAIL: Pre-Specified Efficacy Endpoints

Composite: Stroke / SE / CV Death — Posterior Probability for NI

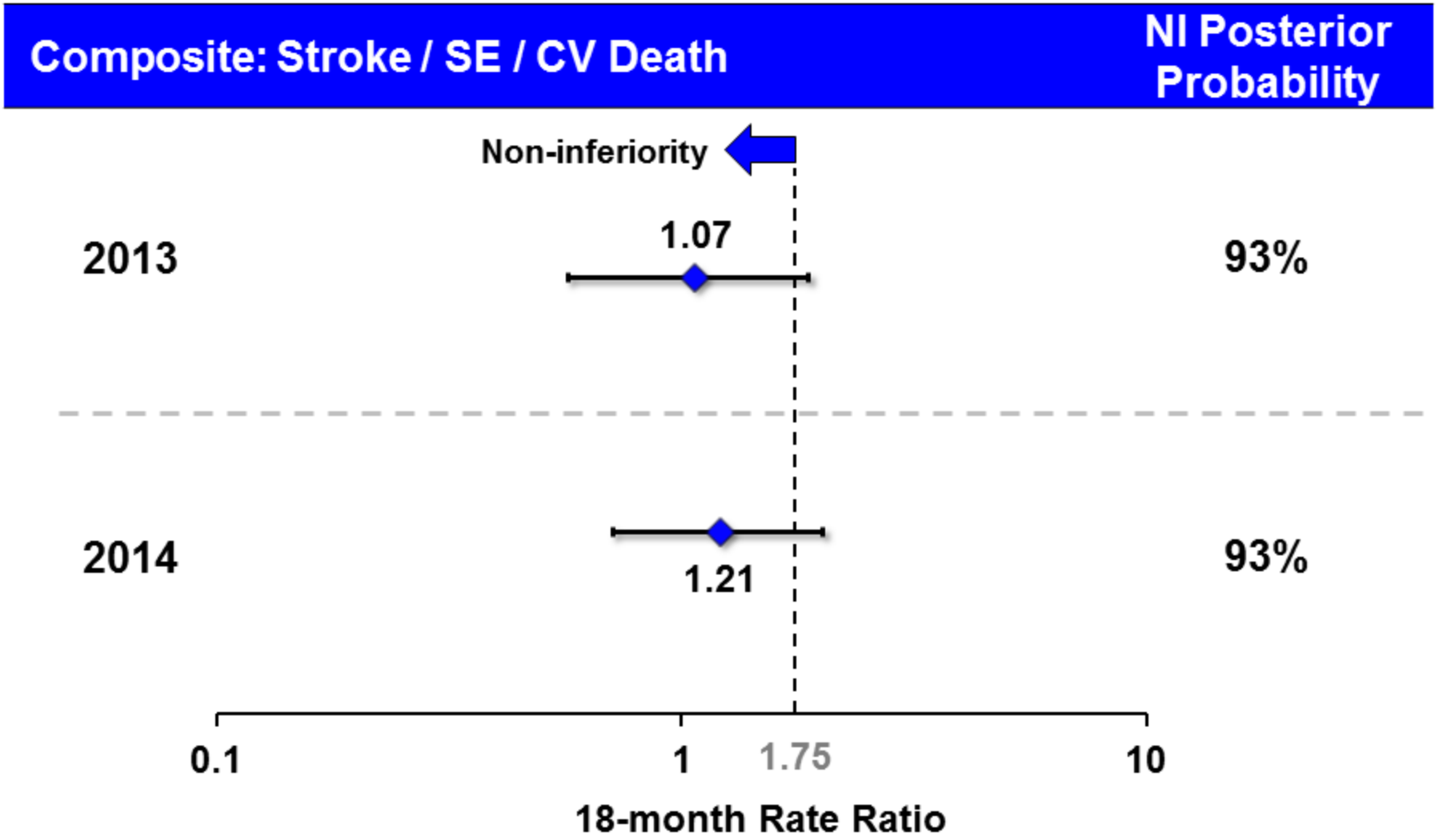


Ischemic Stroke and SE — Posterior Probability for NI



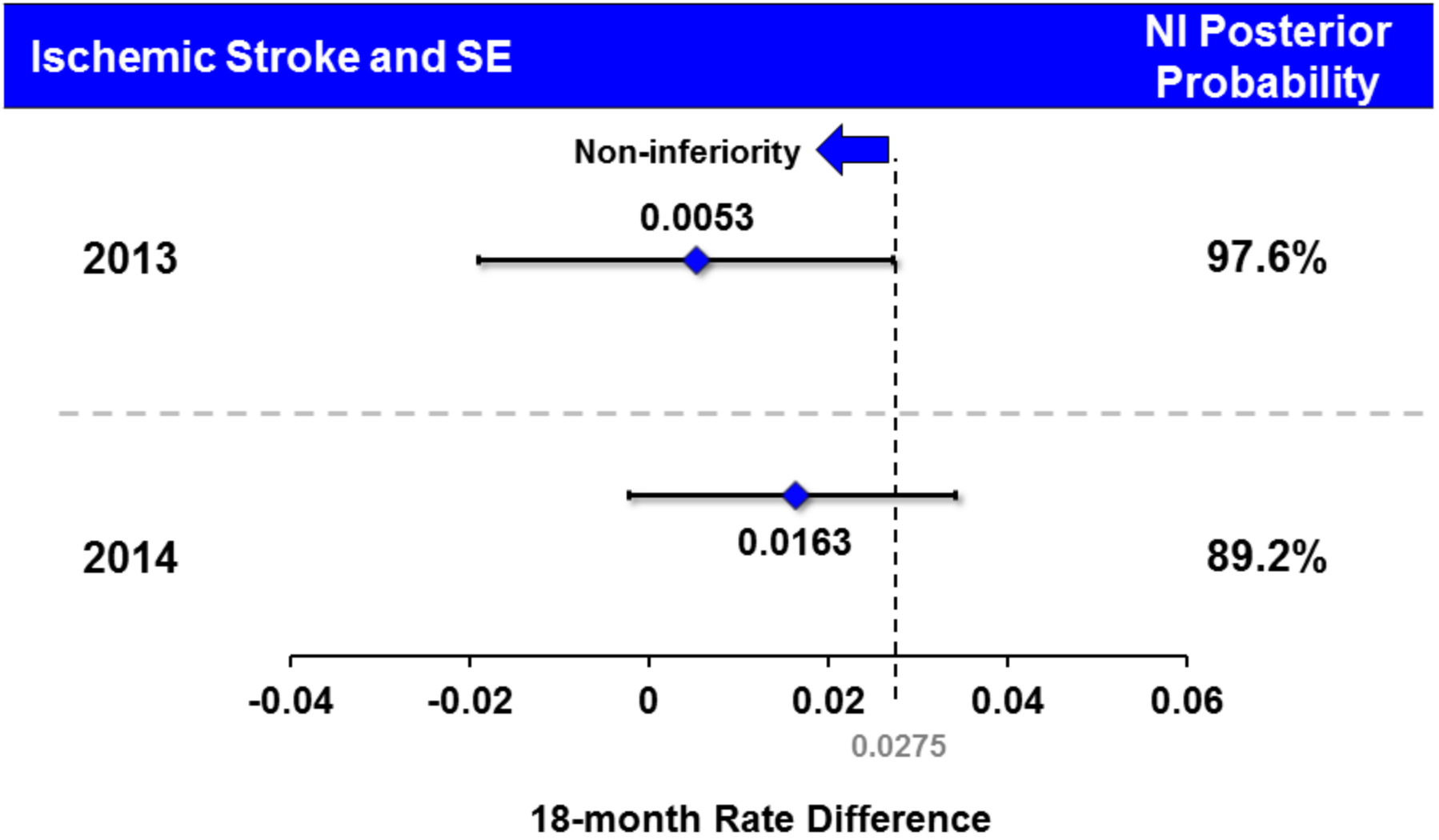
Bayesian model results

PREVAIL Post Hoc Analysis: Efficacy Endpoint Results Same As 2013



Bayesian model results

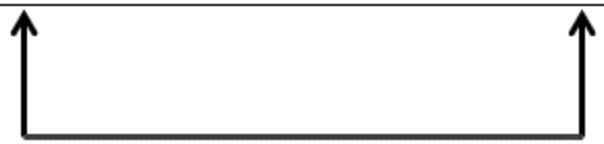
PREVAIL Post Hoc Analysis: Second Endpoint Not Met



Bayesian model results

PREVAIL-only: New Efficacy Events Occur in Same Percentage of Patients

	New First Events Since 2013 Panel			
	WATCHMAN N=269		Warfarin N=138	
Endpoint Event	n	%	n	%
Primary Efficacy	10	3.7	5	3.6



2:1 Randomization

PREVAIL-only: Increase in Ischemic Stroke, Reduction in Hemorrhagic Stroke and CV Death

Endpoint Event	New First Events Since 2013 Panel			
	WATCHMAN N=269		Warfarin N=138	
	n	%	n	%
Primary Efficacy	**10***	**3.7**	**5***	**3.6**
All Stroke	**9**	**3.3**	**2**	**1.4**
Ischemic	**8**	**3.0**	**0**	**0**
Hemorrhagic	**1***	**0.4**	**2***	**1.4**
Systemic Embolism	**0**	**0**	**0**	**0**
Death (CV or Unexplained)	**2***	**0.7**	**4***	**2.9**

* Hemorrhagic stroke followed by death counted as a single event for primary efficacy per the statistical analysis plan

PREVAIL-only: Clinical Detail on New Stroke Events

Patient	Age, Sex	MRS Score Pre	MRS Score Post	Imaging Summary	Outcome
Ischemic Strokes					
WM #1	86 M	0	4	No gross infarct	Home
WM #2	79 M	0	4	Small pontine infarct	Rehab
WM #3	71 M	3	5	Multiple L posterior frontal lobe infarcts	Rehab
WM #4	67 M	0	0	Small R frontal and parietal lobe infarcts	Home
WM #5	63 M	0	1	L posterior frontal lobe infarct	Home
WM #6	84 M	1	1	No gross infarct	Rehab
WM #7	80 M	0	1	L anterior MCA territory infarct	Home
WM #8	77 F	0	1	L thalamic infarct	Home
Hemorrhagic Strokes					
WM #9	81 M	2	6	R frontal hemorrhage 1.9x2.3cm	Death
Warf #1	80 M	1	6	2.3cm R thalamic hemorrhage w/ mass effect	Death
Warf #2	69 M	1	3	Posterior temporal hemorrhage 6x4cm	Rehab

PREVAIL-only: Same Rate of Disabling Strokes Between Randomized Groups

	Event Rate (per 100 pt-yrs)			
	WATCHMAN N=269	Warfarin N=138	Hazard Ratio (95% CI)	p-value
Stroke (all)	**2.7**	**1.0**	**2.64** (0.76, 9.13)	**0.126**
Disabling	**0.7**	**0.7**	**1.14** (0.21, 6.29)	**0.880**
Non-disabling	**1.9**	**0.3**	**5.57** (0.72, 43.20)	**0.101**

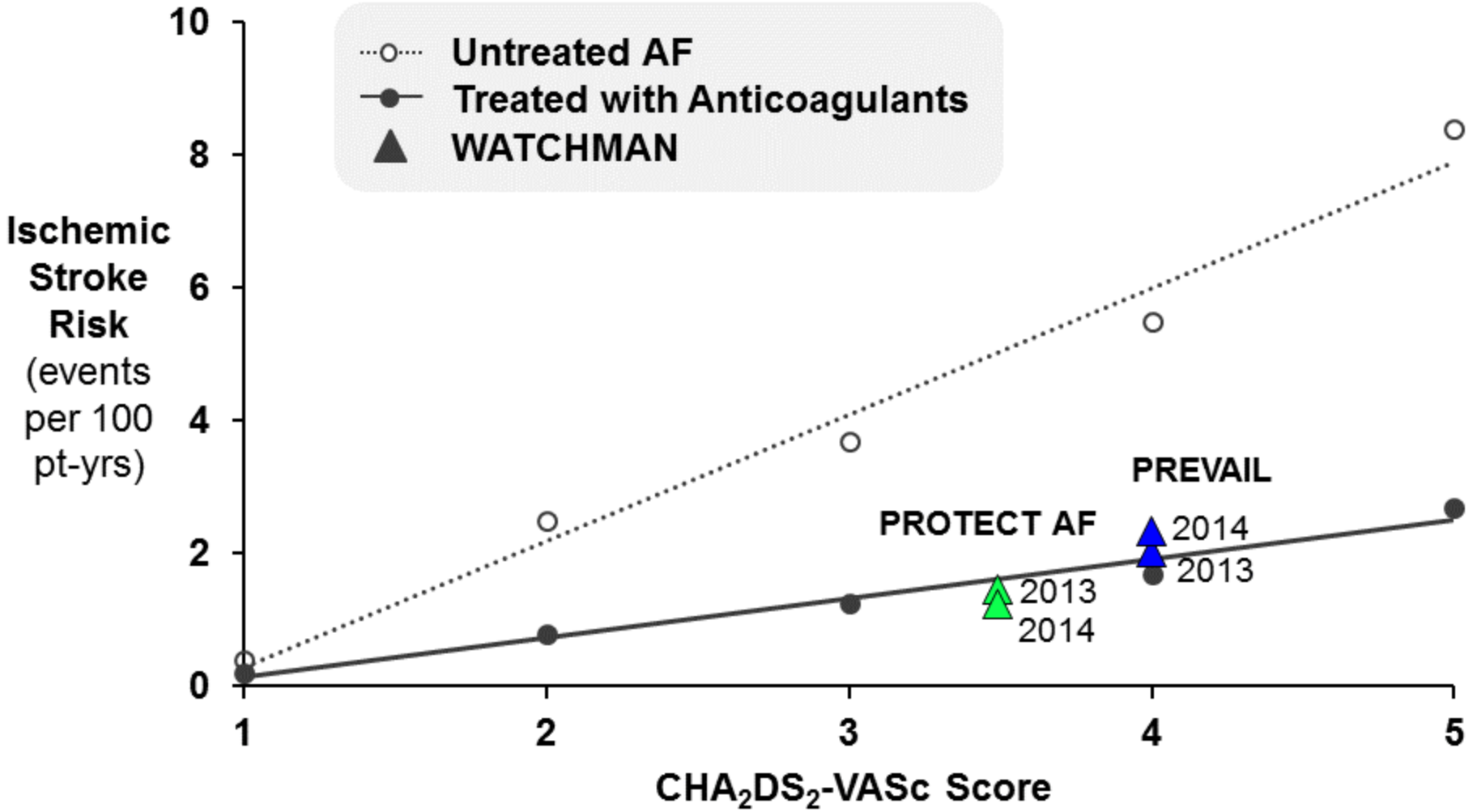
Based on stroke with MRS change of 2 or more or cause of death related to stroke

Proportional Hazards Model

Clinical Results Agenda

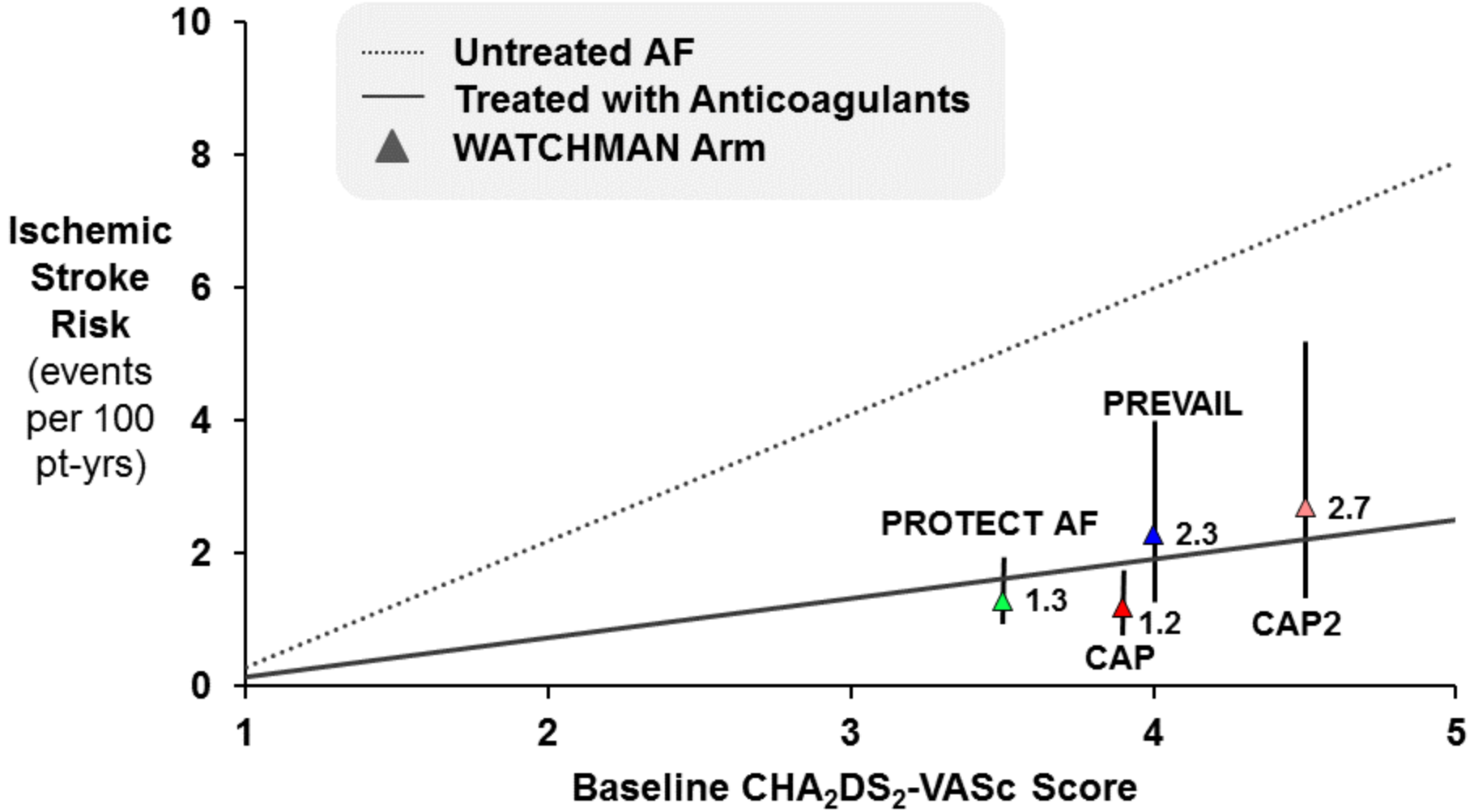
- Procedural safety
- Efficacy in randomized studies
  - PROTECT AF
  - PREVAIL
- Performance consistency
- Totality of evidence

PREVAIL Ischemic Stroke Rate Aligns with Expected Rate Based on Risk Score



Friberg. Eur Heart J (2012); NICE UK (2014)

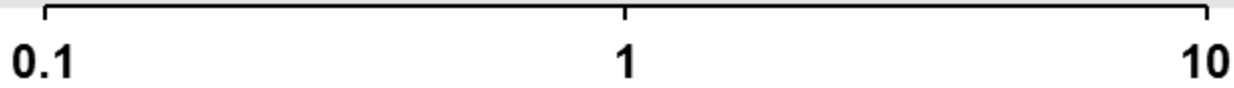
Ischemic Stroke Rate Aligns with Expected Rate Based on Risk Score (All Four Studies)



Friberg. Eur Heart J (2012); NICE UK (2014)

WATCHMAN Primary Efficacy Rate Consistent Across Trials*

Trial (WATCHMAN Arm)	Primary Efficacy Rate per 100 pt-yrs	Mean CHA_2DS_2-VASc
PROTECT AF	2.2	3.5
CAP	2.6	3.9
PREVAIL-only	4.3	4.0
CAP2	3.3	4.5



Rate per Patient-years

*When accounting for CHA_2DS_2 VASc score increase

FDA Requested Analysis: WATCHMAN Reduces Ischemic Stroke Over No Therapy (Imputed)

Study	Average $CHADS_2$ Score WATCHMAN Patients	Observed WATCHMAN Annual Ischemic Stroke Rate (95% CI)	Imputed* Untreated Annual Event Rate	Relative Risk Reduction
PROTECT AF	**2.2**	**1.3** (0.9, 2.0)	**5.6 to 5.7**	**77%** (64%, 84%)
PREVAIL-only	**2.6**	**2.3** (1.3, 4.0)	**6.6 to 6.7**	**65%** (39%, 80%)
CAP	**2.5**	**1.2** (0.8, 1.8)	**6.4**	**81%** (72%, 88%)

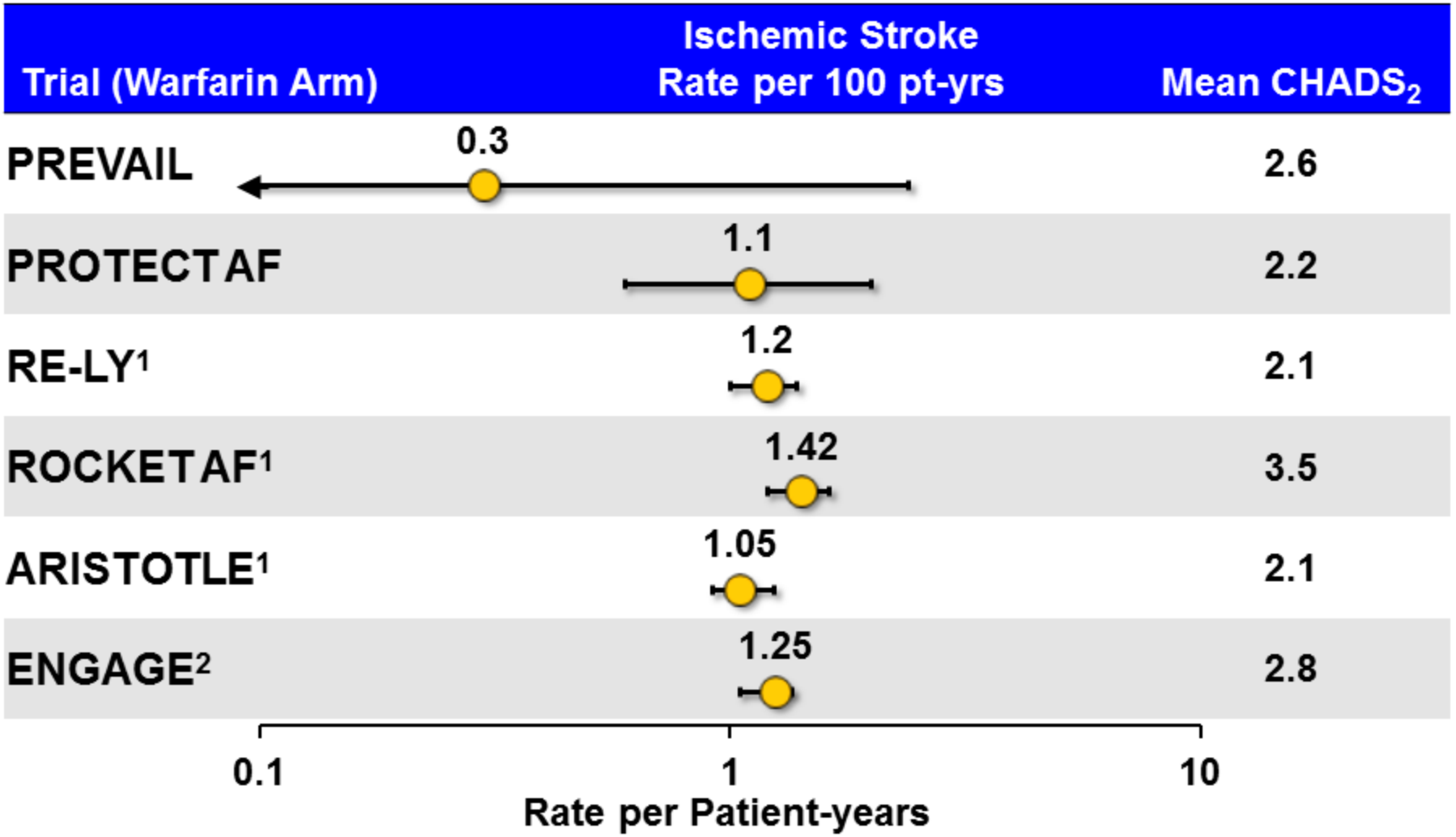
*Gage et al. JAMA (2001); Gage et al. Circulation (2004)

FDA Requested Analysis: WATCHMAN Reduces Ischemic Stroke Over No Therapy (Contemporary Imputed)

	Average CHA_2DS_2-VASC Score	Observed WATCHMAN Ischemic Stroke Event Rate	Imputed* Ischemic Stroke Event Rate	Relative Risk Reduction
PROTECT AF	3.4	1.3	6.2	**79%** (68%, 85%)
PREVAIL-only	3.8	2.3	6.9	**67%** (42%, 81%)
CAP	3.9	1.2	7.1	**83%** (75%, 89%)

* Imputation based on published rate with adjustment for CHA_2DS_2-VASC score (3.0); Olesen JB. Thromb Haemost (2011)

PREVAIL: Warfarin Ischemic Stroke Rate Differs from Other Trials

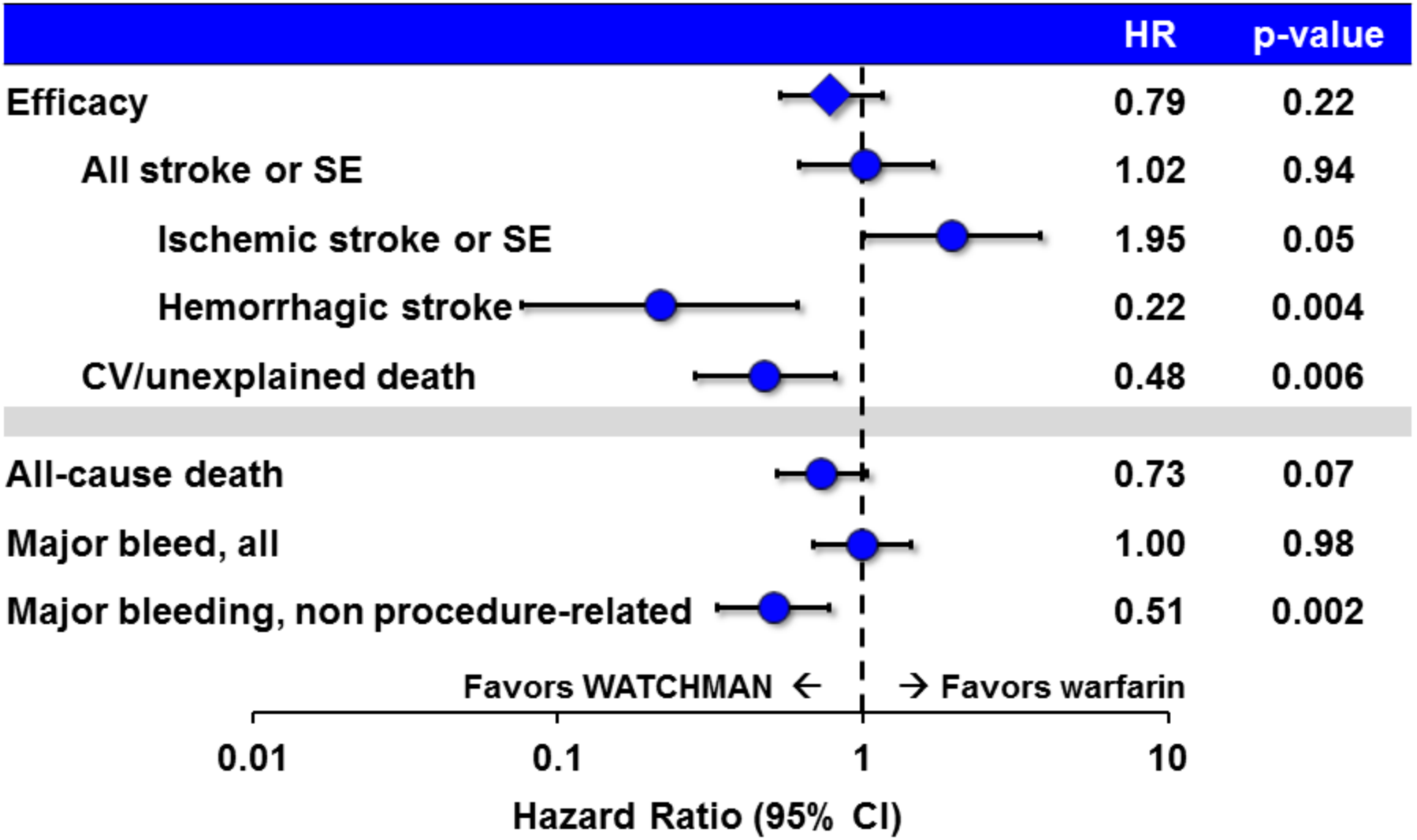


1. Miller. AJC (2012) 2. Giugliano. NEJM (2013)

Clinical Results Agenda

- Procedural safety
- Efficacy in randomized studies
  - PROTECT AF
  - PREVAIL
- Performance consistency
- Totality of evidence

PROTECT AF/PREVAIL Meta-Analysis: WATCHMAN Comparable to Warfarin

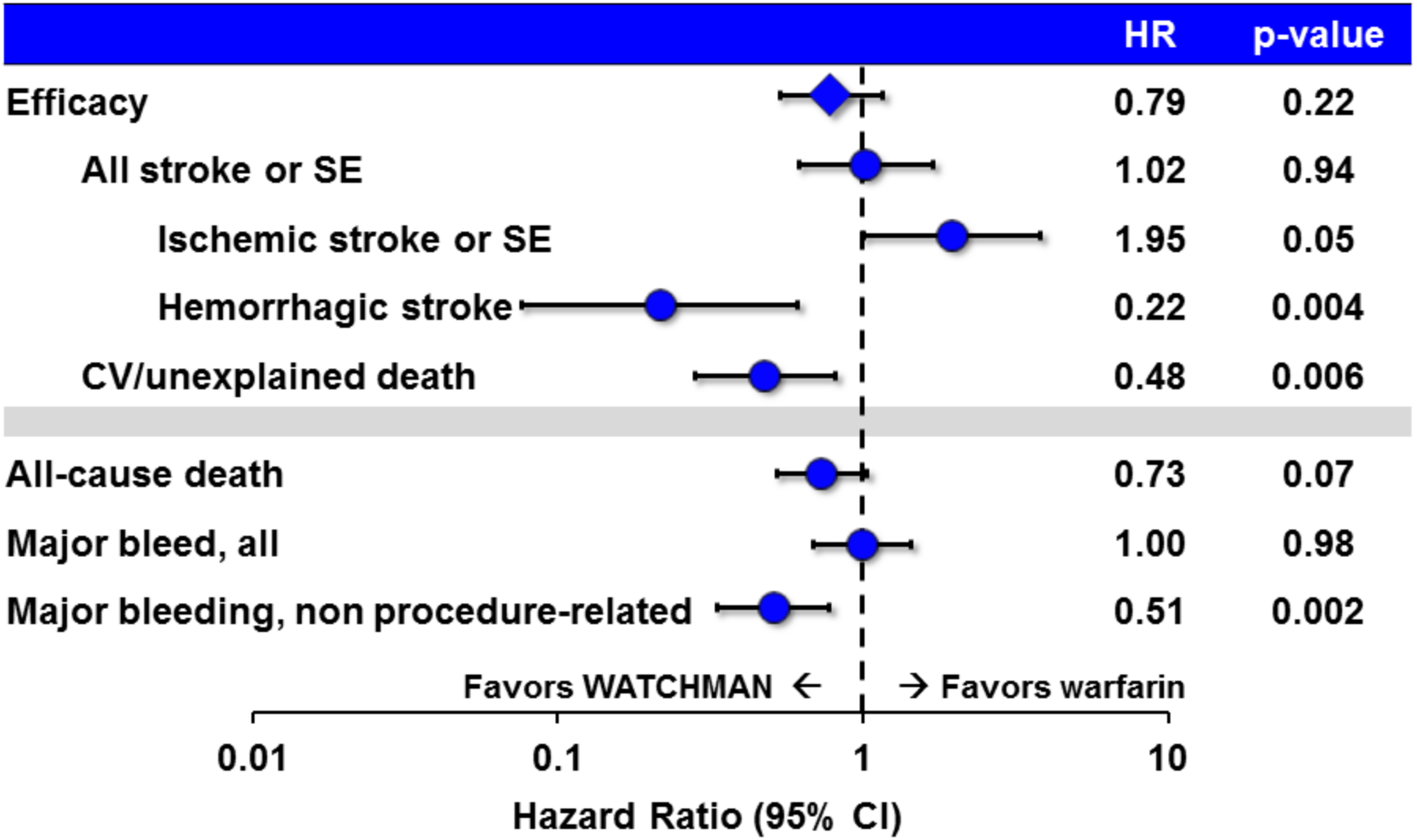


PROTECT AF/PREVAIL Patient-Level Meta-Analysis: Fewer Disabling Strokes with WATCHMAN

	Event Rate (per 100 pt-yrs)			
	WATCHMAN N=732	**Warfarin** N=382	**Hazard Ratio** (95% CI)	**p-value**
Stroke (all)	**1.7**	**1.9**	**1.00** (0.60, 1.67)	**0.991**
Disabling	**0.5**	**1.1**	**0.44** (0.20, 0.98)	**0.044**
Non-disabling	**1.3**	**0.7**	**1.85** (0.88, 3.89)	**0.108**

Based on stroke with MRS change of 2 or more or cause of death related to stroke

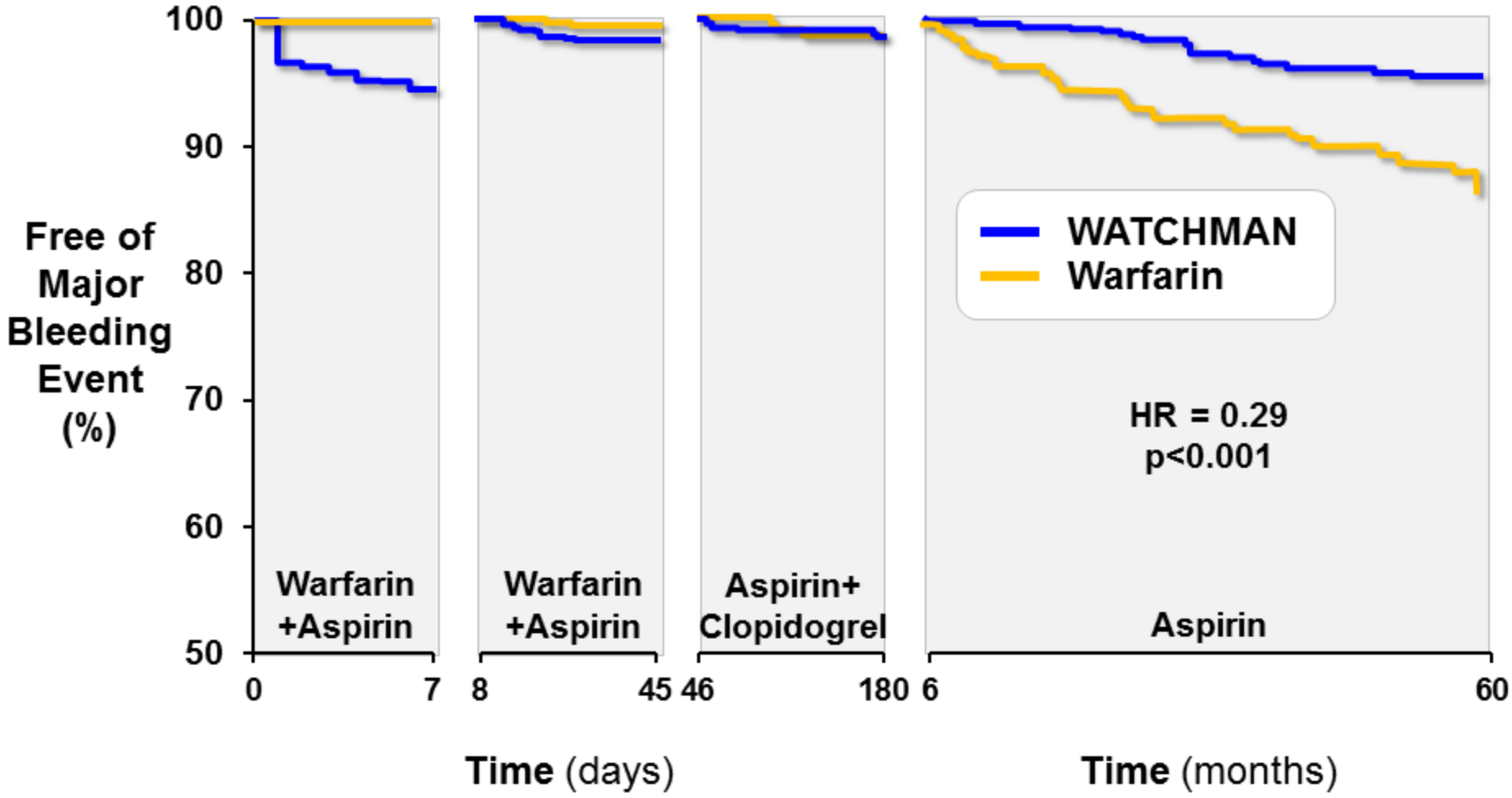
PROTECT AF/PREVAIL Meta-Analysis: WATCHMAN Comparable to Warfarin



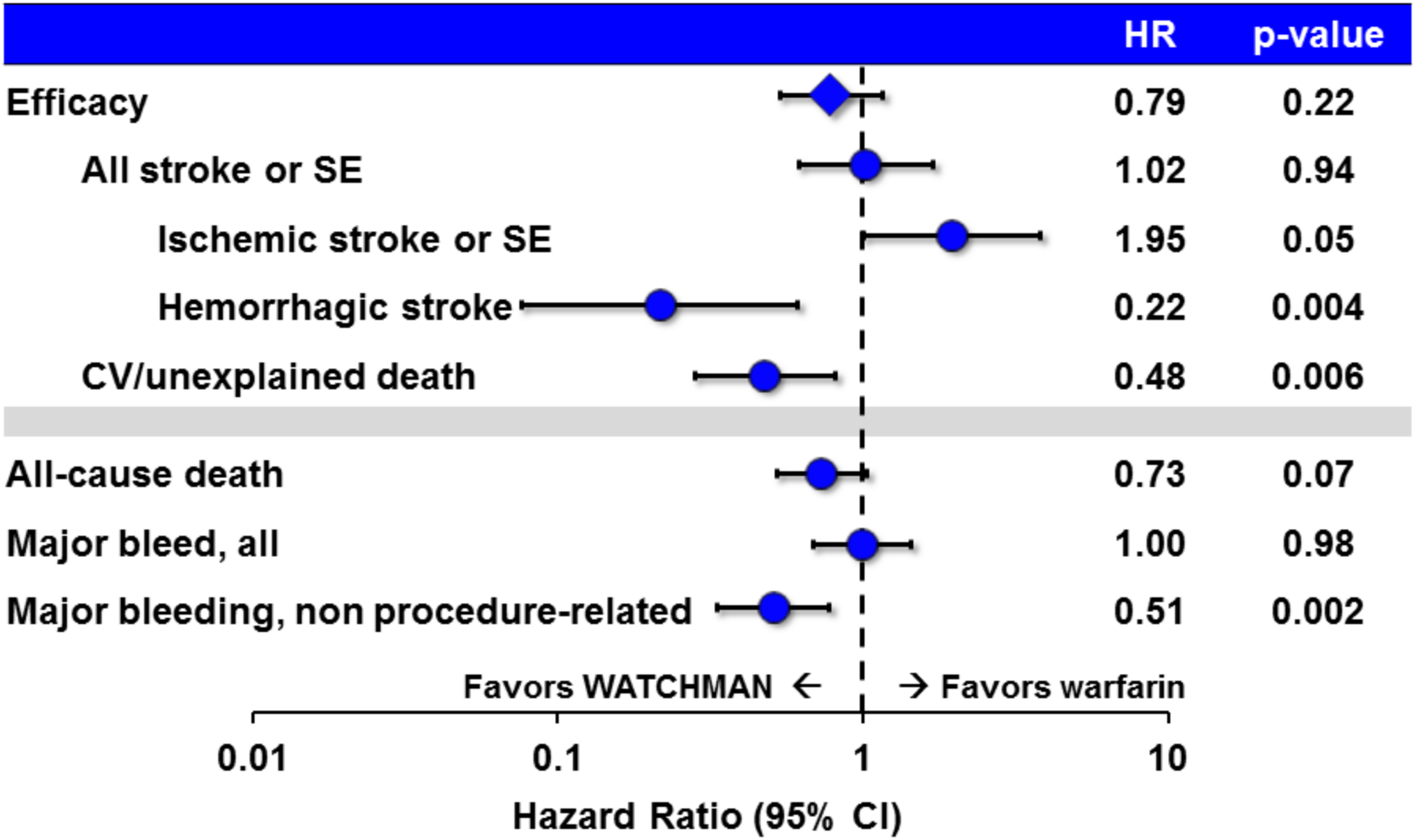
PROTECT AF/PREVAIL: Large Percentage of WATCHMAN Patients Discontinued Warfarin

Warfarin Status	WATCHMAN (PROTECT AF & PREVAIL) N=660	
	N	%
No Long-term Resumption	**591**	**89.5**
No Warfarin Resumption	**547**	**82.9**
Transient Resumption Only	**44**	**6.7**
Long-term Resumption	**41**	**6.2**

PROTECT AF/PREVAIL Meta-Analysis: Less Bleeding with WATCHMAN 6 Months Post-Implant



PROTECT AF/PREVAIL Meta-Analysis: WATCHMAN Comparable to Warfarin



Summary: Totality of Evidence Supports WATCHMAN As Alternative to Warfarin

- Procedural safety - confirmed
- Efficacy in randomized studies
  - PROTECT AF - superior
  - PREVAIL – missed endpoint
- Performance consistency – device performance consistent across trials
- Totality of evidence – meta analysis allows proper weighting

WATCHMAN Comparable Alternative to Warfarin

1. WATCHMAN comparable to warfarin for primary endpoint of stroke, embolization and CV death
2. Ischemic stroke favors warfarin
   - WATCHMAN is superior for hemorrhagic stroke
3. WATCHMAN is superior for disabling stroke
4. WATCHMAN is superior for CV death

Training and Post-Approval Plan

Kenneth Stein, MD
Chief Medical Officer
Rhythm Management
Boston Scientific Corporation

Committed to Safe and Effective Use of Our Products

- Long history of training on novel technologies
  - Endocardial ICD Leads
  - Cardiac Resynchronization Therapy
  - Rotational Atherectomy
  - Subcutaneous ICD

Disciplined Approach to Center Identification Upon Commercialization

- Adequate facilities to perform procedures
- Dedicated team to support procedures including:
  - TEE
  - Anesthesiology
  - Cardiac surgery back-up
  - Center experience in performing other complex cardiac procedures
  - Implanting physician team experienced at, and routinely performing, transseptal punctures

Overview of U.S. WATCHMAN Comprehensive Training Program

- Required of all new implanting teams
  - Implanting physician
  - Echocardiographer
- Four training phases
  - Build on successful PREVAIL training program

Details on U.S. WATCHMAN Comprehensive Training Program

Phase I
Self-Study

- **Online modules**
  - Instructions for Use; Imaging Techniques; Clinical Data; Video Case Studies; Exam

Phase II
Professional Training Event

- **Mandatory professional training event**
- **Experienced WATCHMAN physician faculty**
- **Use of virtual reality tools**
- **Patient selection**
- **Patient-centric decision making**

Phase III
Initial Cases

- **First cases supported by Clinical Specialist**
- **Optional physician proctors**

Phase IV
Transition to Independence

- **Ongoing case support**

Enhanced Post-Approval Study Design

- 1,000 new patients
  - Up to an additional 579 CAP2 patients
- 5-year, non-randomized study
  - Success defined against pre-specified performance goals
- Prospective analysis of bleeding complications
- Strategies to recruit more diverse patients

Summary of Post-approval Activities

- Center selection
- Comprehensive training program
- Roll-out cadence
- Post-approval study

Benefit-risk and Conclusion

Kenneth Huber, MD

President and CEO, Saint Luke's Mid America Heart Institute, CV Consultants

Professor of Medicine

University of Missouri, Kansas City

Benefit-risk Assessment for AF Patients

- Challenges of benefit-risk assessment for an individual patient
- Limitations of current treatment options
- Evidence supports LAA closure with WATCHMAN as a clinically acceptable alternative to long-term warfarin therapy

Difficult to Strike Balance in Stroke and Bleeding Risk

CHA_2DS_2-VASc* Score	Annual % Stroke Risk
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7

HAS-BLED** Score	Annual % Bleed Risk
0	0.9
1	3.4
2	4.1
3	5.8
4	8.9
5	9.1

* 2014 AHA / ACC / HRS Guidelines
** Lip. JACC (2011)

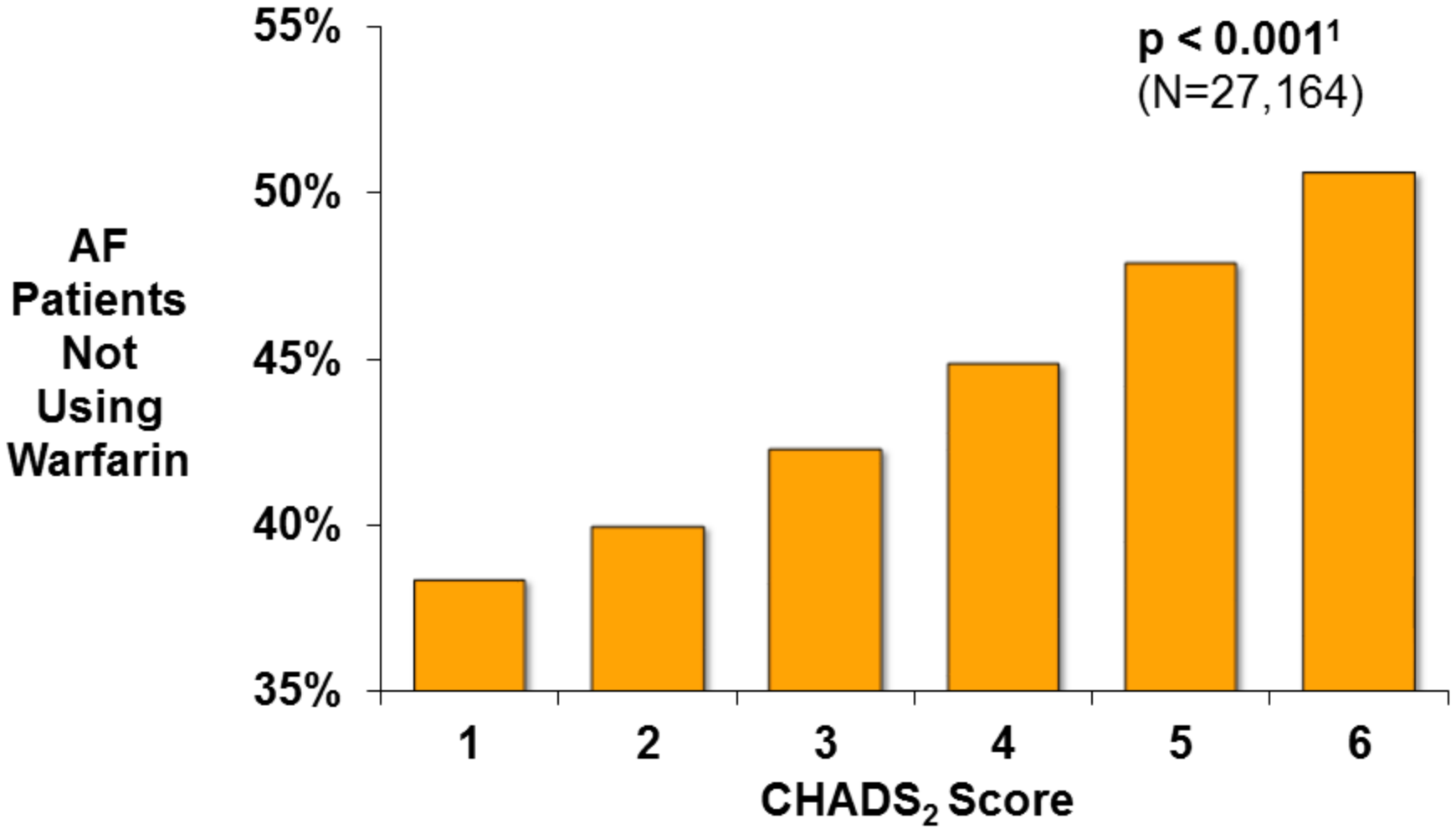
Bleeding Risk Increases Over Patients' Lifetime

HAS-BLED Score	Annual % Bleed Risk*	10-Year Bleeding Risk (%)**
0	0.9	8.6
1	3.4	29.2
2	4.1	34.2
3	5.8	45.0
4	8.9	60.6
5	9.1	61.5

* Lip. JACC (2011)

** Assumes constant risk despite increasing age and bleeding risk is independent from bleeding risk in previous years

High-risk Patients Unprotected



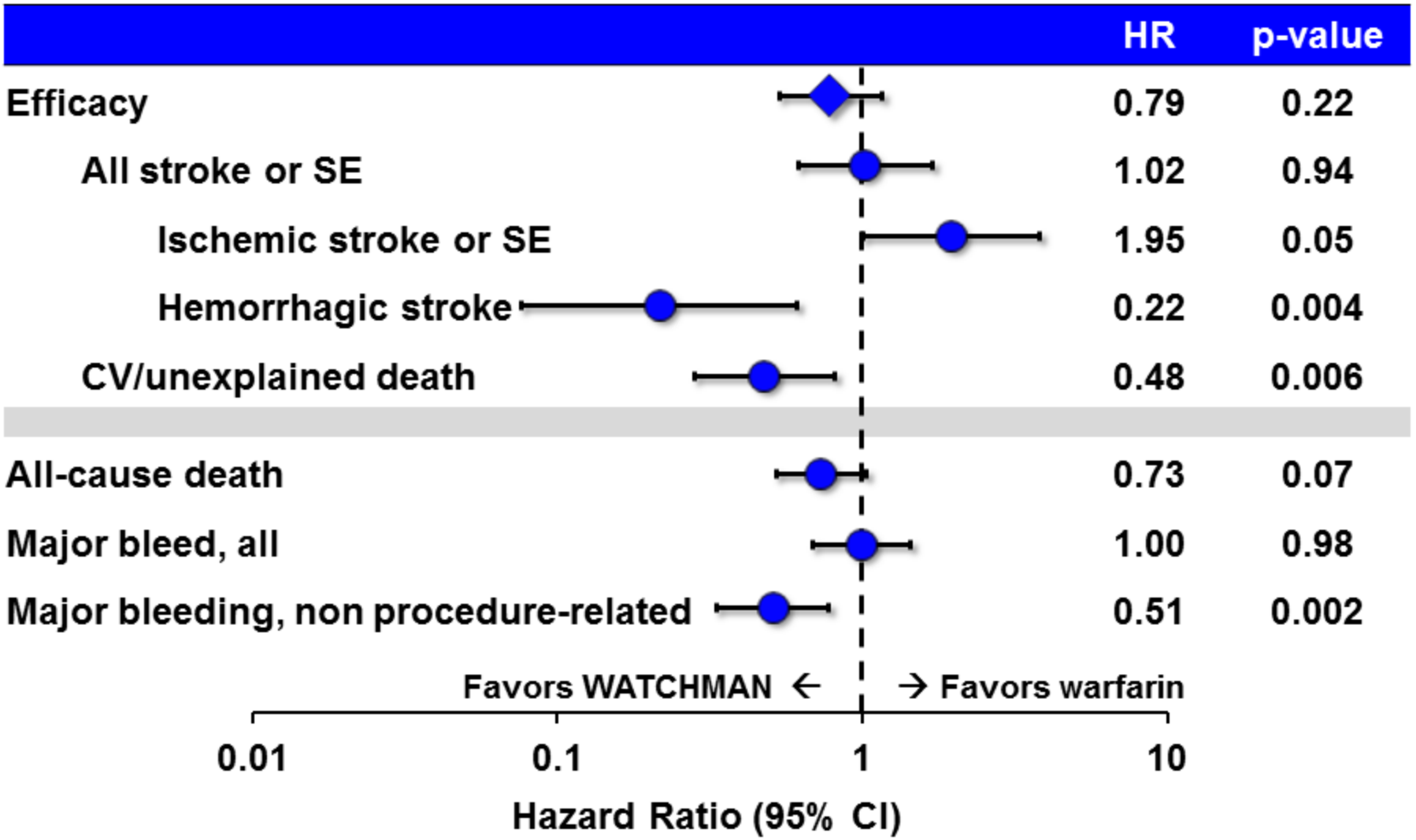
1. Piccini. Heart Rhythm (2012)

Current Alternative Therapies for Unprotected Patients

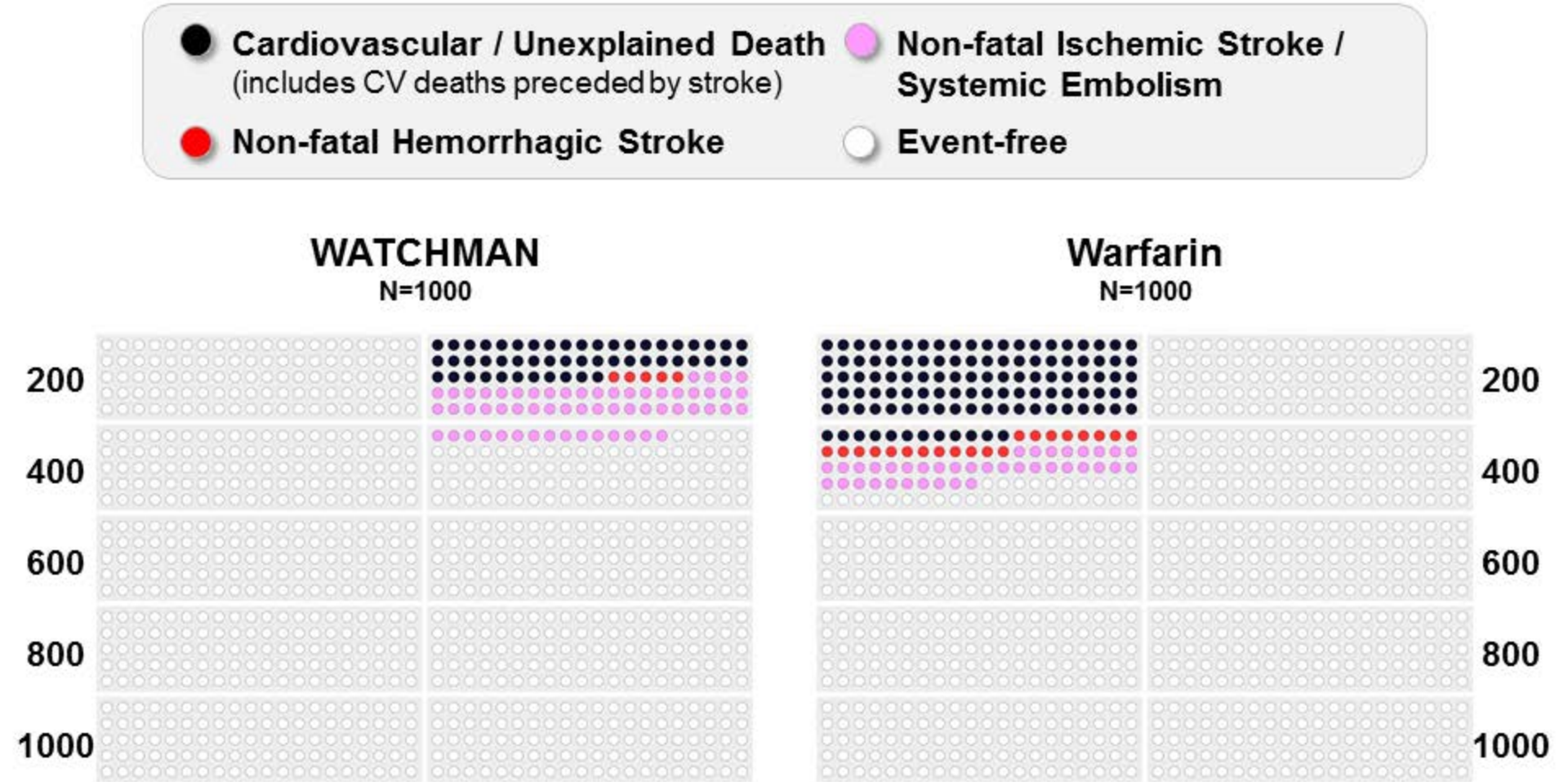
- Anti-platelet therapies: inferior[1]
- Procedure-based
  - LAA-ligation/Lariat: no RCT data
  - Open cardiothoracic surgery: no RCT data

1. Cooper et al. Arch Intern Med (2006)

PROTECT AF/PREVAIL Meta-Analysis: WATCHMAN Comparable to Warfarin



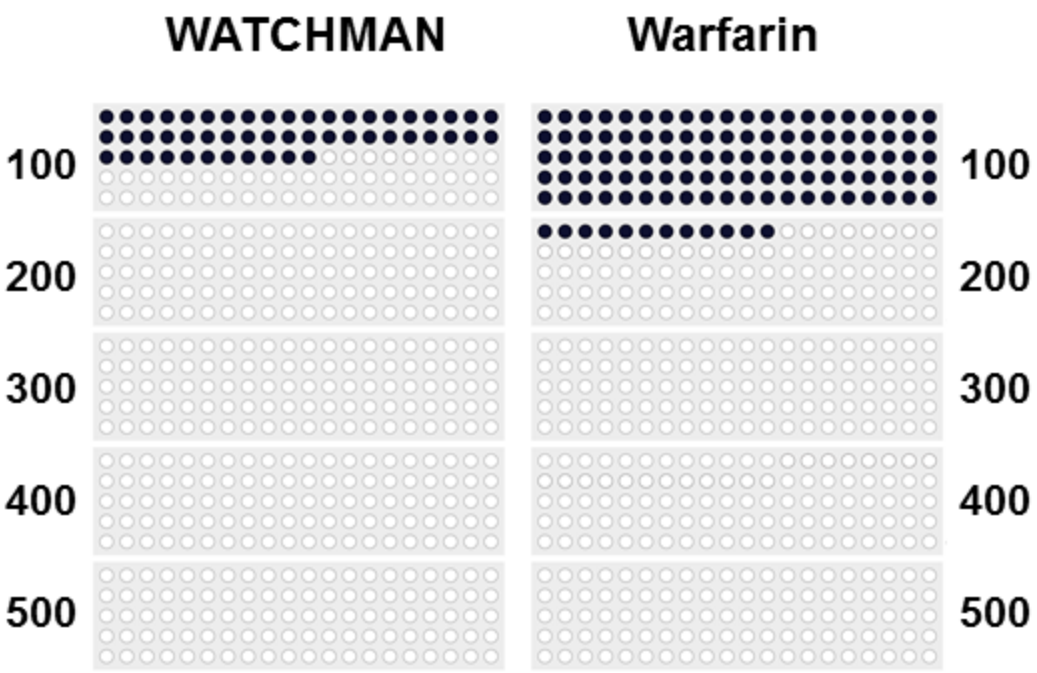
WATCHMAN Comparable to Warfarin for Primary Efficacy



N=1000; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years

Cardiovascular Death Lower with WATCHMAN vs. Warfarin

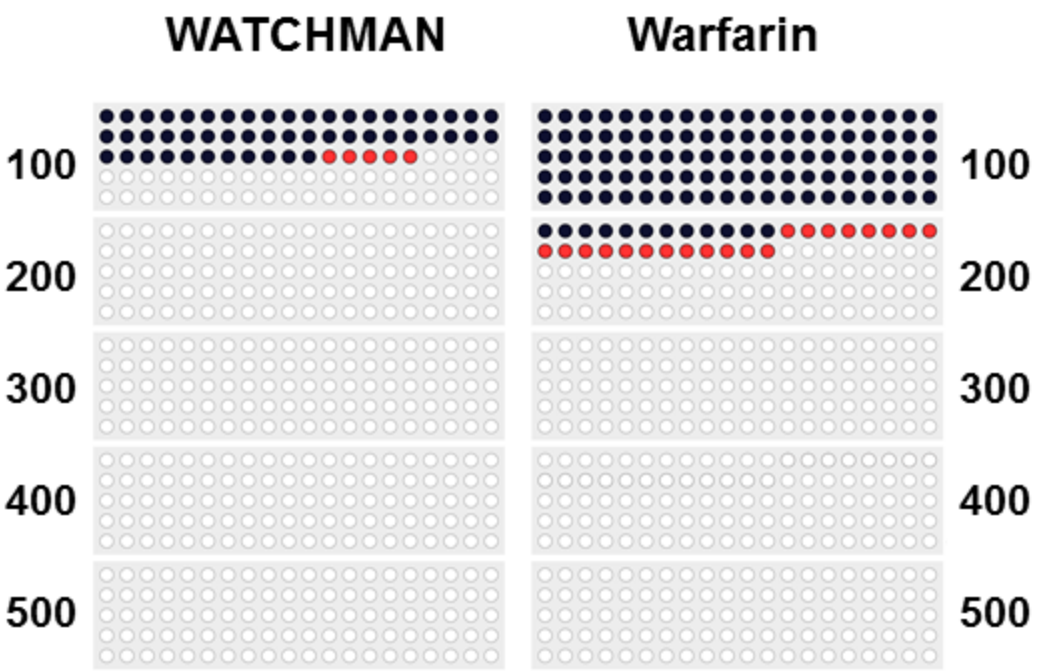
- Cardiovascular / Unexplained Death (includes CV deaths preceded by stroke)
- Non-fatal Ischemic Stroke / Systemic Embolism
- Non-fatal Hemorrhagic Stroke
- Event-free



Zoomed in to show N=500 of 1000 patients for each study arm; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years

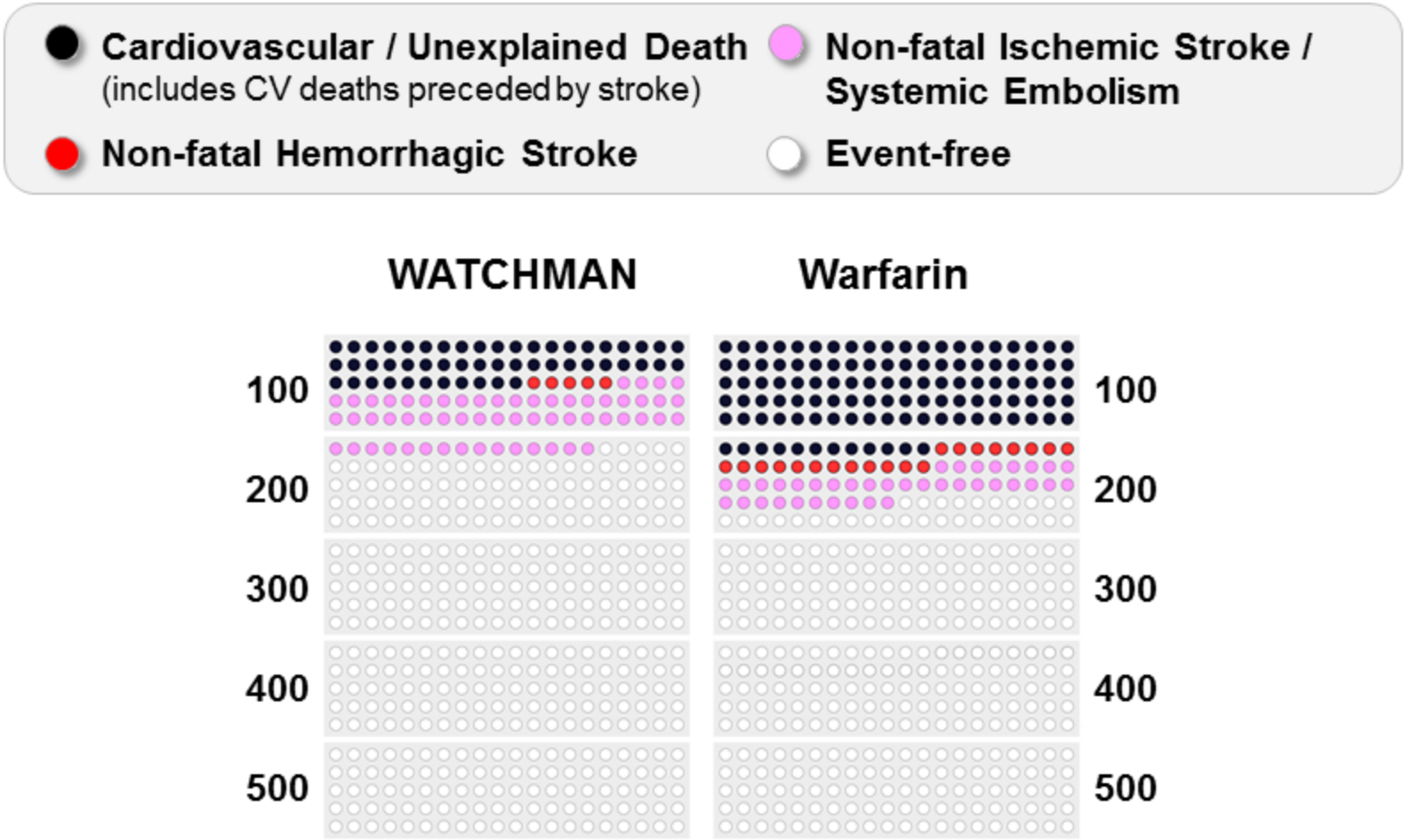
Hemorrhagic Stroke Lower with WATCHMAN vs. Warfarin

- Cardiovascular / Unexplained Death (includes CV deaths preceded by stroke)
- Non-fatal Ischemic Stroke / Systemic Embolism
- Non-fatal Hemorrhagic Stroke
- Event-free



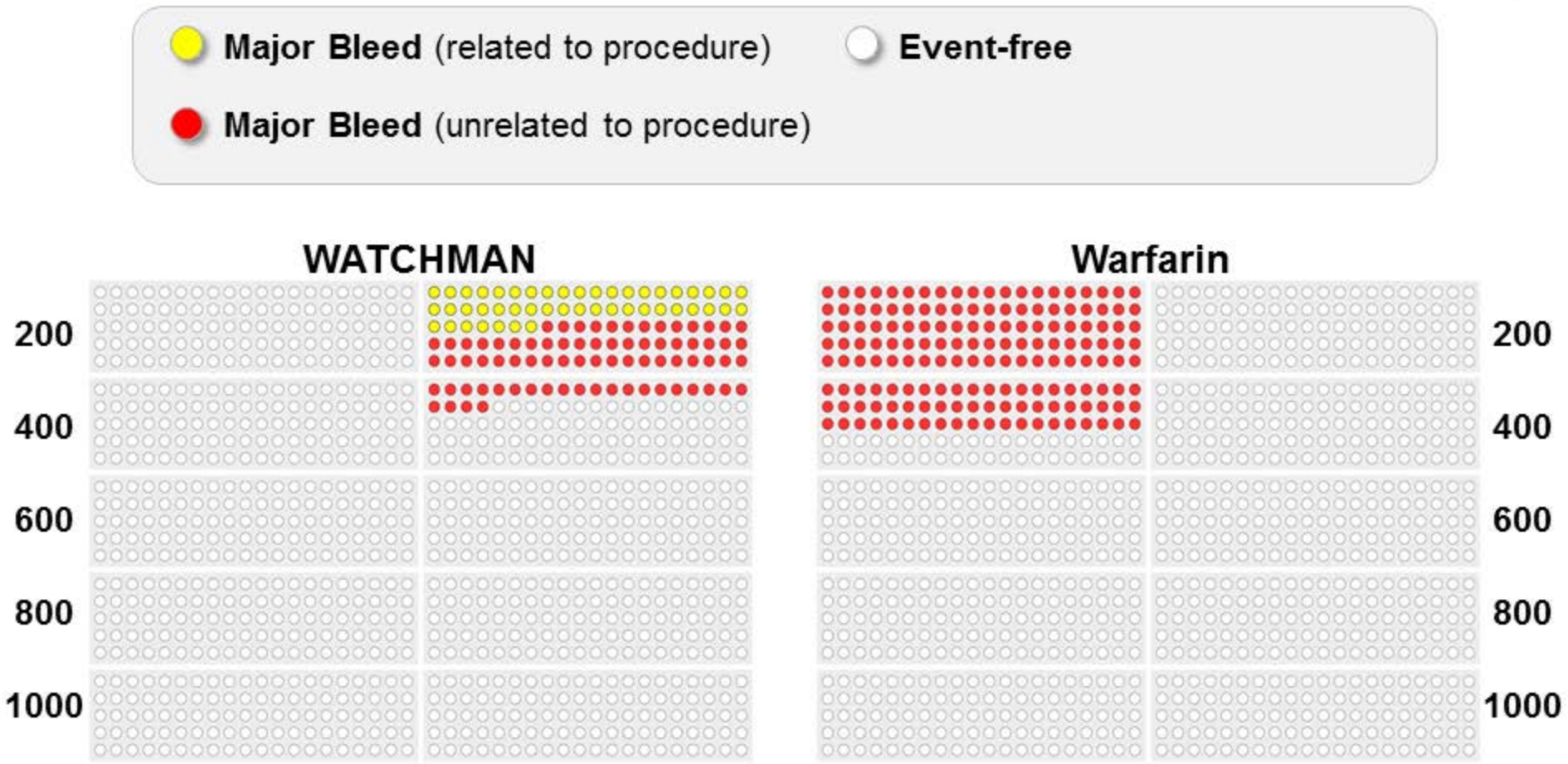
Zoomed in to show N=500 of 1000 patients for each study arm; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years

Ischemic Stroke/SE Lower with Warfarin vs. WATCHMAN



Zoomed in to show N=500 of 1000 patients for each study arm; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years

WATCHMAN Performs Better than Warfarin for Major Bleeding

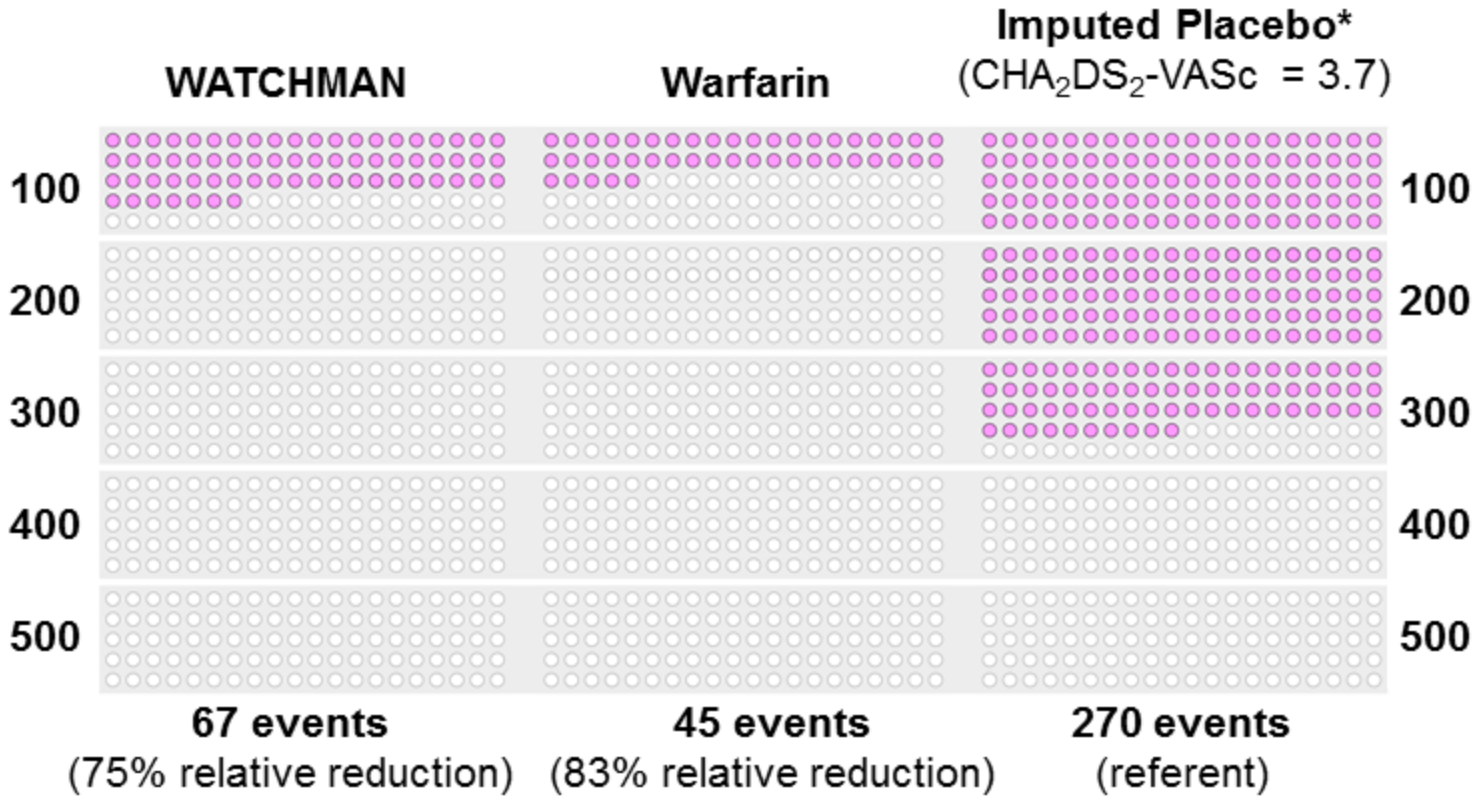


N=1000; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years

WATCHMAN and Warfarin Reduce Ischemic Stroke vs. No Therapy

Ischemic Stroke / Systemic Embolism
(includes fatal and non-fatal events)

Free of Ischemic Stroke



Zoomed in to show N=500 of 1000 patients for each study arm; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years; *Friberg. Eur Heart J (2012)

WATCHMAN is a Clinically Acceptable Alternative to Long-Term Warfarin

- Need alternative, evidence-based therapies for patients with AF who have a rationale not to take warfarin long-term
- Totality of data support WATCHMAN as comparable to warfarin
- Data unequivocally support LAA closure with WATCHMAN as a clinically acceptable alternative to warfarin for appropriate patients

WATCHMAN Left Atrial Appendage Closure (LAAC) Technology for Patients with Non-valvular Atrial Fibrillation (AF)

October 8, 2014

Boston Scientific Corporation

FDA Circulatory System Devices Panel

Backup Slides Shown

PREVAIL: Rationale for Warfarin + Aspirin Therapy at Study Entry

Rationale for Warfarin + Aspirin Therapy	WATCHMAN N=269	Warfarin N=138
Coronary Artery Disease (CAD)	70	45
History of Stroke/TIA	19	12
Other		
Suspected CAD, angina, chest pain	2	2
Anticoagulation, atrial fibrillation	6	0
Preventive care	5	1
Physician preference/prescribed	5	1
Miscellaneous	6	0
Peripheral Vascular Disease	1	5
Total	114 (42.4%)	66 (47.8%)

MRS Data Collection

- Baseline
- 45 day office visit
- 6 months
- 9 months
- 12 months
- 18 months
- 30 months
- 2-5 year annual visit

PROTECT and PREVAIL: Time from Stroke to MRS

Time from Stroke to MRS (days)	PROTECT AF	PREVAIL
Median	66	87
IQR	43, 134	32, 109

Panel 2013:Warfarin Cessation Rates High in WATCHMAN Patients

	PROTECT AF (N=408)		CAP (N=534)		PREVAIL (N=253)	
Visit	n/N	%	n/N	%	n/N	%
45-day	348 / 401	86.8	507 / 529	95.8	227 / 246	92.2
6-month	355 / 385	92.2	493 / 500	98.6	235 / 239	98.3
12-month	345 / 370	93.2	455 / 472	96.4	141 / 142	99.3

2013/2014 Panel: Components of First Efficacy Primary Endpoint (PREVAIL)

	PREVAIL – only (2013 Panel)		PREVAIL – only (2014 Panel)		Total New Events Since 2013 Panel	
	WATCHMAN Events	Warfarin Events	WATCHMAN Events	Warfarin Events	WATCHMAN Events	Warfarin Events
Primary Efficacy	14	4	24	10	10	5
Stroke						
Ischemic	5	1	13	1	8	0
Hemorrhagic	1	0	2	2	1*	2*
Systemic Embolism	1	0	1	0	0	0
CV Death	7	3	8	6	2*	4*

* Hemorrhagic stroke followed by death counted as a single event for primary efficacy per the statistical analysis plan

PREVAIL-only: Primary Efficacy Rates

Endpoint Event	Event Rate (per 100 pt-yrs) WATCHMAN N=269	Warfarin N=138	HR (95%CI)	P-value
Composite Primary Efficacy	4.3	3.0	1.41 (0.65, 3.03)	0.383
Individual Components				
All Stroke	2.7	1.0	2.61 (0.76, 9.01)	0.130
Ischemic	2.3	0.3	6.82 (0.89, 52.15)	0.064
Hemorrhagic	0.4*	0.7*	0.52 (0.07, 3.66)	0.508
Systemic Embolism	0.2	0	N/A	N/A
Death (CV or Unexplained)	1.4*	2.3*	0.71 (0.25, 2.05)	0.527

* Hemorrhagic stroke followed by death counted as a single event for primary efficacy per the statistical analysis plan

Warfarin Time in Therapeutic Range (TTR) for Control Groups

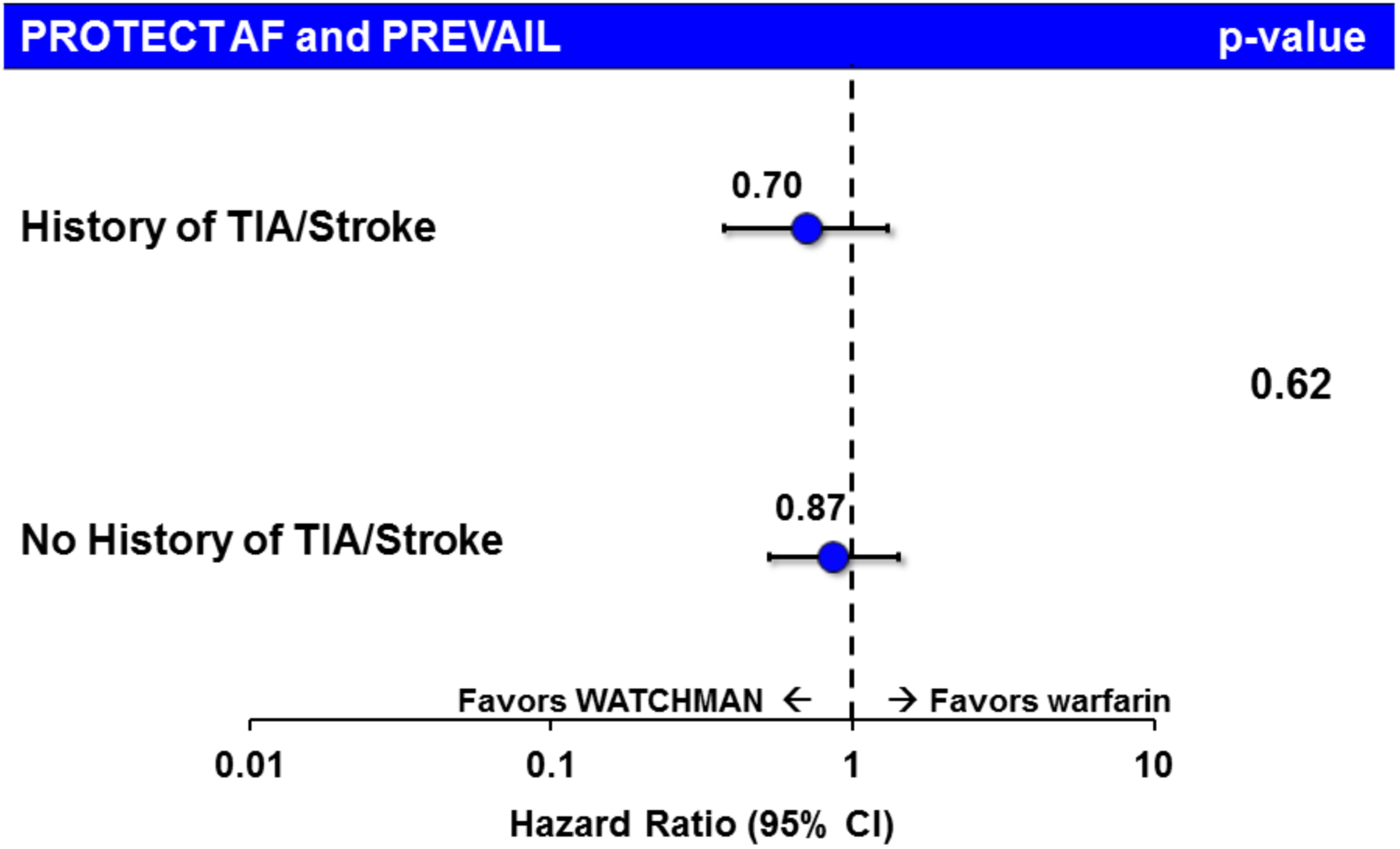
Study	Warfarin Control Group Mean TTR
PROTECT AF	**70%**
PREVAIL	**68%**
ENGAGE AF[1] (Edoxaban)	**68%**
RE-LY[2] (Dabigatran)	**64%**
ARISTOTLE[3] (Apixaban)	**62%**
ROCKET AF[4] (Rivaroxaban)	**55%**

1. Giugliano RP et al. NEJM (2013)
2. Connolly SJ et al. NEJM (2009)
3. Granger CB et al. NEJM, (2011)
4. Patel MR, et al. NEJM, (2011)

Device-related Thrombus PROTECT, CAP, and PREVAIL

	PROTECT AF (N=408)	CAP (N=534)	PREVAIL (N=252)
Thrombus Subjects	**16 (3.9%)**	**12 (2.2%)**	**15 (6.0%)**
Thrombus Events	**17**	**19**	**16**
Experienced Ischemic Stroke	**2**	**1**	**1**
Experienced Serious Adverse Event	**3**	**1**	**1**
Annual Device Thrombus-related Stroke Rate (per 100 pt-yrs)	**0.1**	**0.05**	**0.2**

Patient-Level Meta-Analysis: Efficacy Hazard Ratios by Stroke/TIA



Panel 2014: PREVAIL Causes of Death

Category	WATCHMAN N=269		Control N=138		p-value
	n	%	n	%	
Cardiovascular	8	3.0	7	5.1	0.28
Heart failure	0	0	1	0.7	0.34
Hemorrhagic stroke	1	0.4	1	0.7	1.00
Ischemic stroke	0	0	0	0	1.00
Myocardial infarction	2	0.7	0	0	0.55
Sudden death	6	2.2	5	3.6	0.52
Cancer	4	1.5	2	1.5	1.00
Pulmonary	6	2.2	2	1.5	0.72
Multisystem Organ Failure	0	0	0	0	1.00
Neurologic	0	0	0	0	1.00
Renal Failure	1	0.4	0	0	1.00
Sepsis	0	0	1	0.7	0.34
Other	2	0.7	1	0.7	1.00

PREVAIL: Cardioversion by Visit

Days from Randomization	WATCHMAN		Warfarin		
	n/N	%	n/N	%	p-value
0 – 30 days	3 / 259	1.2	2 / 132	1.5	0.766
31 – 44 days	4 / 259	1.5	3 / 132	2.3	0.608
45 days	7 / 259	2.7	5 / 132	3.8	0.556
6 months	8 / 239	3.3	5 / 129	3.9	0.793
9 months	3 / 233	1.3	2 / 124	1.6	0.803
12 months	4 / 234	1.7	3 / 119	2.5	0.605
18 months	10 / 225	4.4	4 / 118	3.4	0.639
24 months	4 / 208	1.9	1 / 96	1.0	0.574
30 months	1 / 127	0.8	1 / 67	1.5	0.644
36 months	1 / 61	1.6	1 / 26	3.8	0.530
Total (per-patient)*	26 / 269	9.7	15 / 138	10.9	0.702

*Patients may have multiple cardioversions

PREVAIL: Ablations Reported At Follow-Up Visit

Days from Randomization	WATCHMAN		Warfarin		p-value
	n/N	%	n/N	%	
45 days	0 / 259	0.0	3 / 132	2.3	0.015
6 months	6 / 239	2.5	7 / 129	5.4	0.148
9 months	3 / 233	1.3	2 / 124	1.6	0.803
12 months	2 / 234	0.9	1 / 119	0.8	0.989
18 months	5 / 225	2.2	4 / 118	3.4	0.520
24 months	2 / 208	1.0	2 / 96	2.1	0.425
30 months	2 / 127	1.6	1 / 67	1.5	0.965
36 months	0 / 61	0.0	1 / 26	3.8	0.123
Total (per-patient)*	18 / 269	6.7	17 / 138	12.3	0.055

*Patients may have multiple ablations

Warfarin in non-cardioembolic stroke

- **Warfarin-Aspirin Recurrent Stroke Study (WARSS)**
- Multicenter, double-blinded, randomized trial at 48 centers in US with ischemic CVA in prior 30 days – randomized to ASA or warfarin
- Primary endpoint:
  - recurrent ischemic stroke or death from any cause in 2 years
  - observed in Warfarin (17.8%) and aspirin (16%) – p=0.25, HR 1.13, 95% CI 0.92-1.38
- There was **no difference between warfarin and ASA** in preventing recurrent ischemic stroke

Mohr JP. N Engl J Med 2001;345:1444-51

Warfarin vs. ASA for Symptomatic Intracranial Arterial Stenosis

- **WASID Trial**
- 569 US patients with prio **TIA or CVA caused by angiographically-verified stenosis 50-99% of major extracranial artery**
- Randomized to receive **warfarin (INR 2-3) or ASA (1300mg daily)**
- **Primary endpoint**
  - Composite ischemic stroke, brain hemorrhage, death from vascular cause other than stroke
  - Occurred in **22% ASA group and 21.8% warfarin group (HR 1.04; 95% CI 0.7-1.48, p=0.83)**
- **Warfarin provided no benefit over aspirin**, but warfarin patients experienced significantly higher rates of AEs and the trial was stopped early as a result.

Chimowitz MI. N Engl J Med 2005;352:1305-16

Table 47: 2013/2014 Panel: Components of First Efficacy Primary Endpoint (PREVAIL)

Type	PREVAIL-only (2013 Panel)		PREVAIL-only (2014 Panel)		Total New Events since 2013 Panel	
	WATCHMAN (N Events/ % of pts)	Warfarin (N Events/ % of pts)	WATCHMAN (N Events/% of pts)	Warfarin (N Events/ % of pts)	WATCHMAN (N Events/% of pts)	Warfarin (N Events/% of pts)
Primary Efficacy	14 (5.2%)	4 (2.9%)	24 (8.9%)	10 (7.2%)	**10 (3.7%)**	**5 (3.6%)**
Stroke – Ischemic	5 (1.9%)	1 (0.7%)	13 (4.8%)	1 (0.7%)	**8 (3.0%)**	**0 (0.0%)**
Stroke – Hemorrhagic	1 (0.4%)	0 (0.0%)	2 (0.7%)	2 (1.4%)	**1 (0.4%)**	**2 (1.4%)**
Systemic embolism	1 (0.4%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	**0 (0.0%)**	**0 (0.0%)**
Death – CV and Unexplained	7 (2.6%)	3 (2.2%)	8 (3.0%)	6 (4.3%)*	**1 (0.4%)**	**4 (2.9%)***

*There was one Warfarin Group patient who had a hemorrhagic stroke followed by death. This was only counted as a single event for the combined primary endpoint, per the SAP.

CEC Adjudication of Stroke Type Hemorrhagic Event Definitions

	PROTECT AF	PREVAIL
Hemorrhagic Stroke	Sudden onset of a focal neurological deficit with CT or MRI evidence of tissue loss with evidence of blood vessel hemorrhage.	Symptomatic (focal neurological deficit) intracranial hemorrhage due to any cause.
Other Definitions	Subdural Hematoma: A traumatic hemorrhage limited to the subdural compartment is defined as a "cranial bleed" and not as a stroke.	Intracranial Bleed: Asymptomatic intracranial hemorrhage.

Using these definitions:

- **3 PROTECT AF Warfarin Group patients** had SDH's that were also adjudicated as hemorrhagic strokes (no device group patients)
- **1 PREVAIL WATCHMAN Group patient** had a SDH that was also adjudicated as a hemorrhagic stroke (no warfarin group patients)

Hemorrhagic Stroke and Cranial Bleeds

PROTECT AF	WATCHMAN N=463	Warfarin N=244	p-value*
Hemorrhagic Stroke	3	10	0.002
Non-hemorrhagic Stroke Intracranial Bleeding	5	1	0.439
Total	8	11	0.047
Percent of Randomized Subjects	8/463 = 1.7%	11/244 = 4.5%	

* Fisher's exact test

Panel 2014: PREVAIL Causes of Death

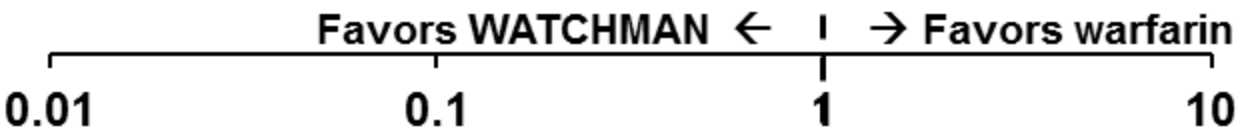
Category	WATCHMAN N=269		Control N=138		p-value
	n	%	n	%	
Cardiovascular	9	3.4	7	5.1	0.40
Heart failure	0	0	1	0.7	0.34
Hemorrhagic stroke	1	0.4	1	0.7	1.00
Ischemic stroke	0	0	0	0	1.00
Myocardial infarction	2	0.7	0	0	0.55
Sudden death	6	2.2	5	3.6	0.52
Cancer	4	1.5	2	1.5	1.00
Pulmonary	6	2.2	2	1.5	0.72
Multisystem Organ Failure	0	0	0	0	1.00
Neurologic	0	0	0	0	1.00
Renal Failure	1	0.4	0	0	1.00
Sepsis	0	0	1	0.7	0.34
Other	2	0.7	1	0.7	1.00

All WATCHMAN Trials: Baseline LVEF

Characteristic	WATCHMAN N=732	Warfarin N=382	p-value
LVEF, mean ± SD	56.63 ± 9.85	56.45 ± 9.99	0.7784

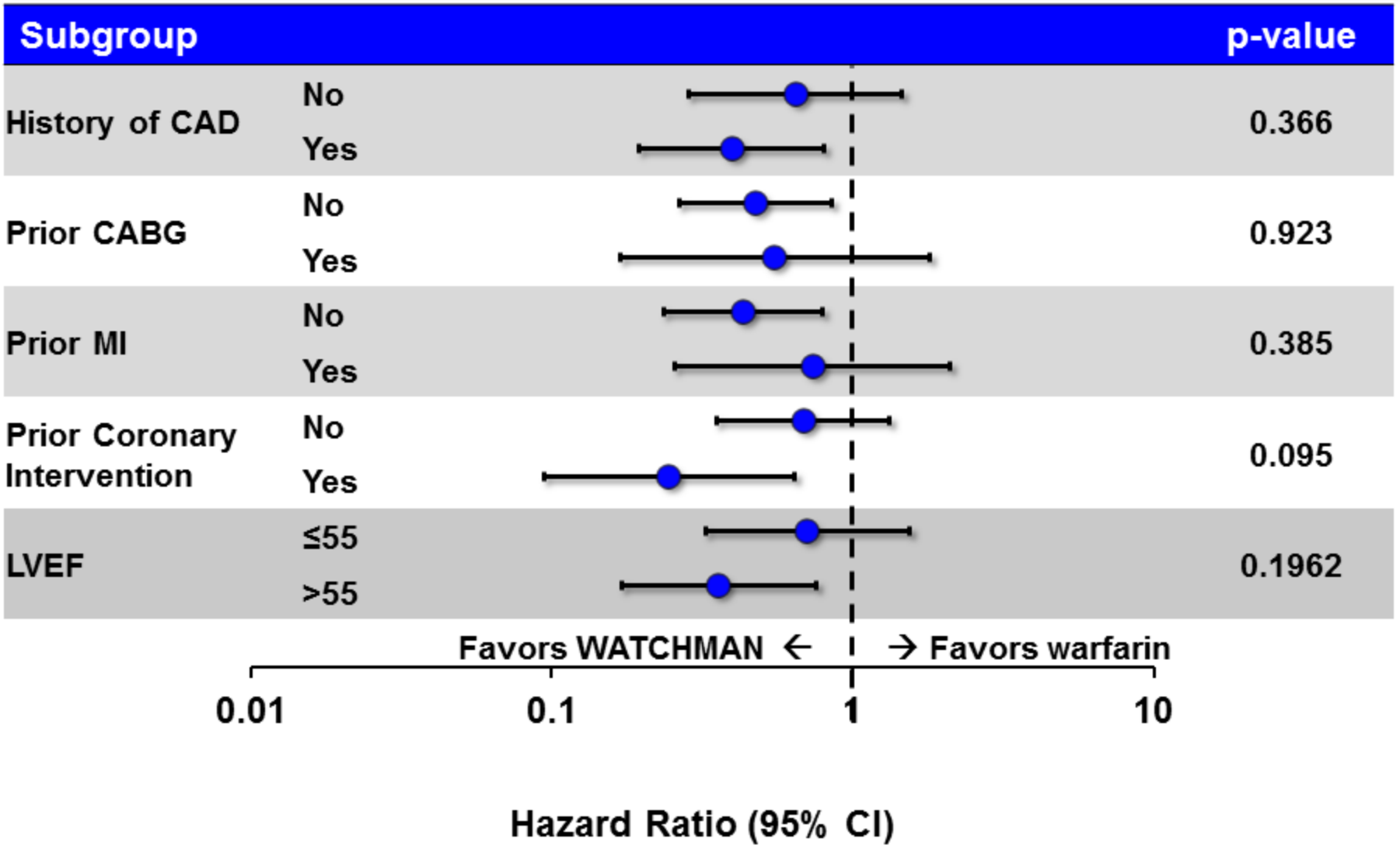
Pooled PROTECT AF and PREVAIL: Efficacy Endpoint by Risk Factors

Subgroup		p-value
History of CAD	No	0.837
	Yes	
Prior CABG	No	0.881
	Yes	
Prior MI	No	0.606
	Yes	
Prior Coronary Intervention	No	0.831
	Yes	
LVEF	≤55	0.1962
	>55	

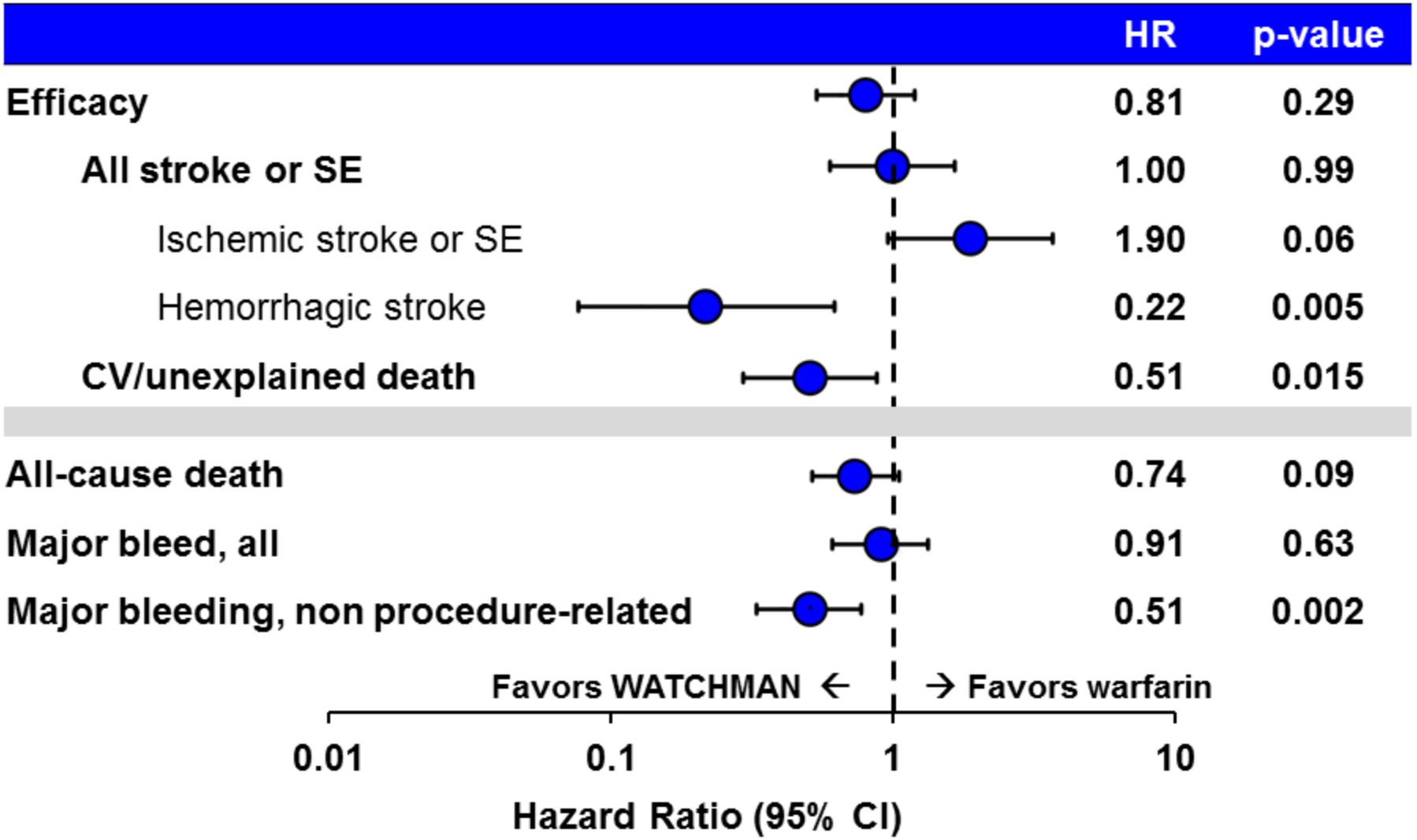


Hazard Ratio (95% CI)

Pooled PROTECT AF and PREVAIL: CV/Unexplained Death by Risk Factors

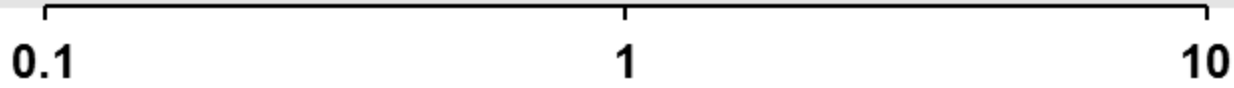


PROTECT AF-PREVAIL-like/PREVAIL Meta-Analysis: WATCHMAN Comparable to Warfarin



WATCHMAN Primary Efficacy Rate Consistent Across Trials*

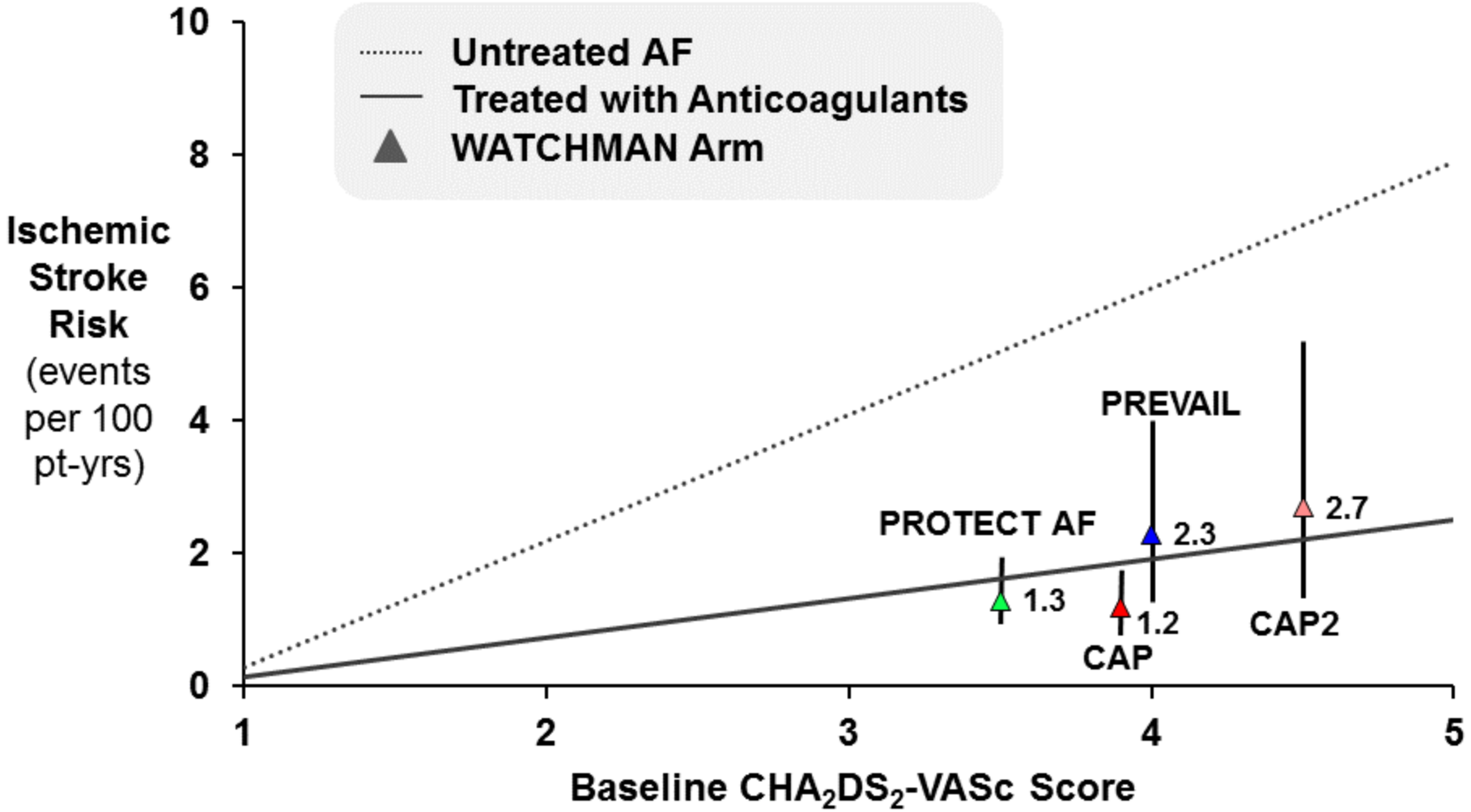
Trial (WATCHMAN Arm)	Primary Efficacy Rate per 100 pt-yrs	Mean CHA_2DS_2-VASc
PROTECT AF	2.2	3.5
CAP	2.6	3.9
PREVAIL-only	4.3	4.0
CAP2	3.3	4.5



Rate per Patient-years

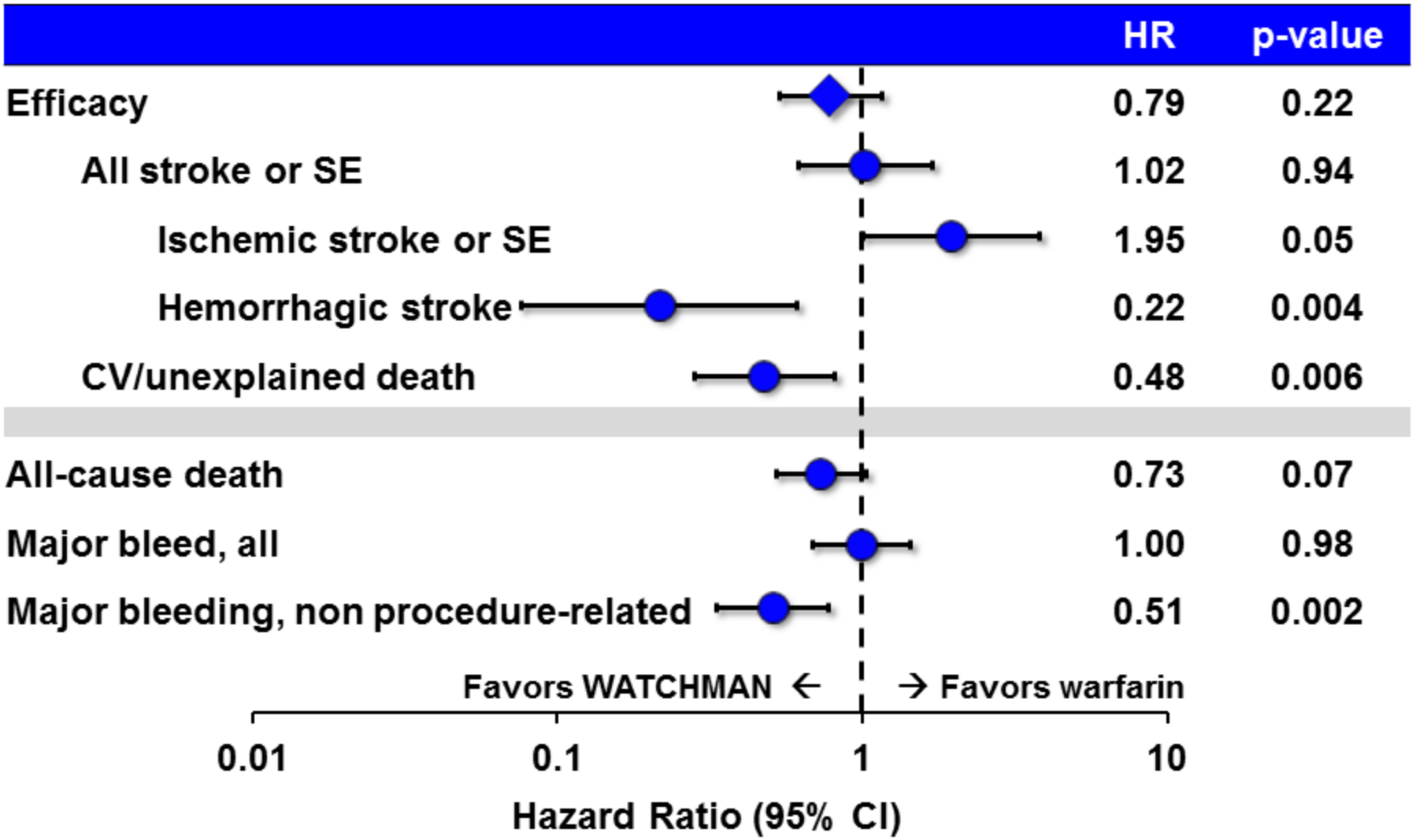
*When accounting for CHA_2DS_2 VASc score increase

Ischemic Stroke Rate Aligns with Expected Rate Based on Risk Score (All Four Studies)



Friberg. Eur Heart J (2012); NICE UK (2014)

PROTECT AF/PREVAIL Meta-Analysis: WATCHMAN Comparable to Warfarin

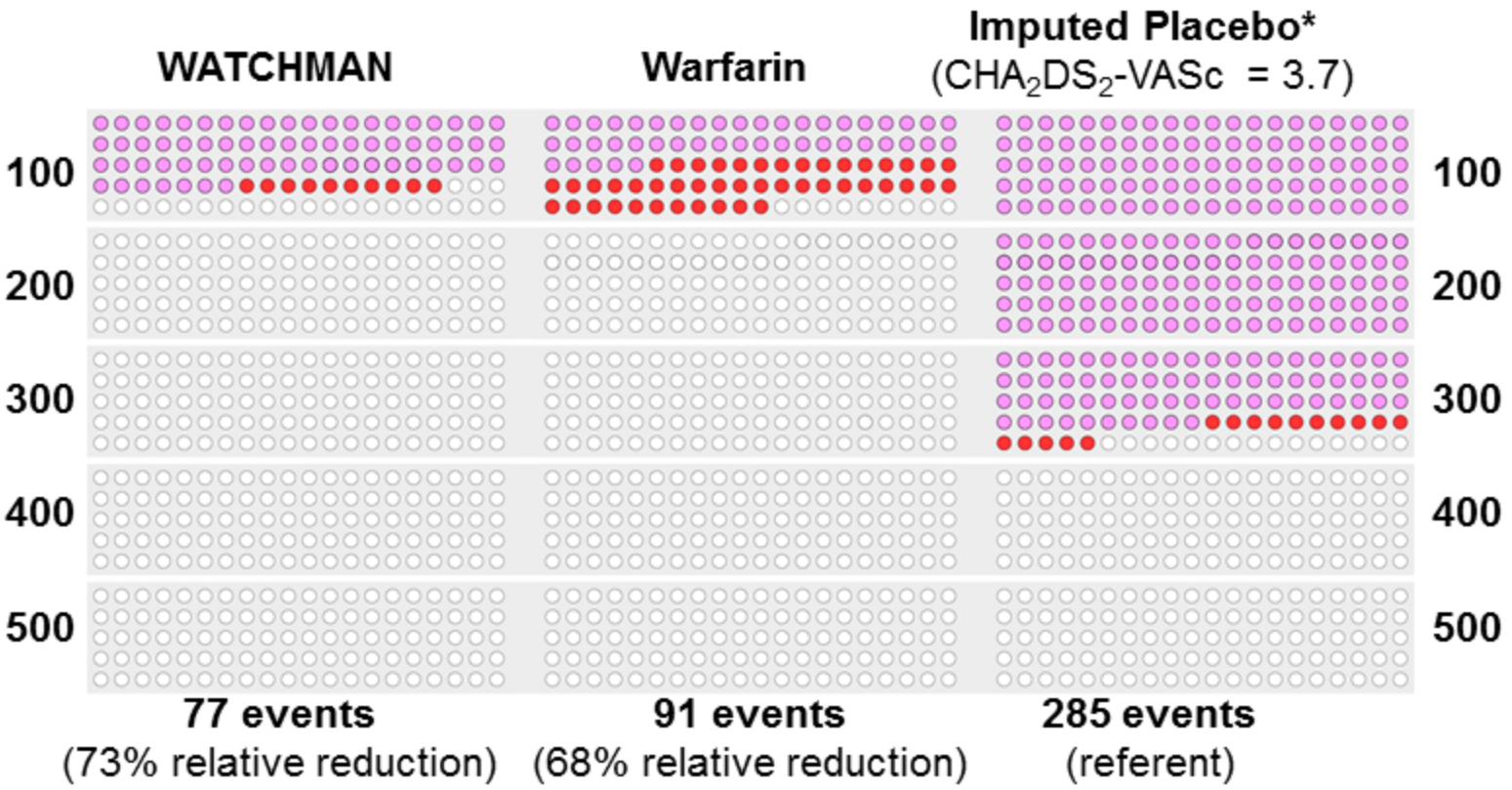


WATCHMAN Reduces Ischemic and Hemorrhagic Stroke vs No Therapy

Ischemic Stroke / Systemic Embolism
(includes fatal and non-fatal events)

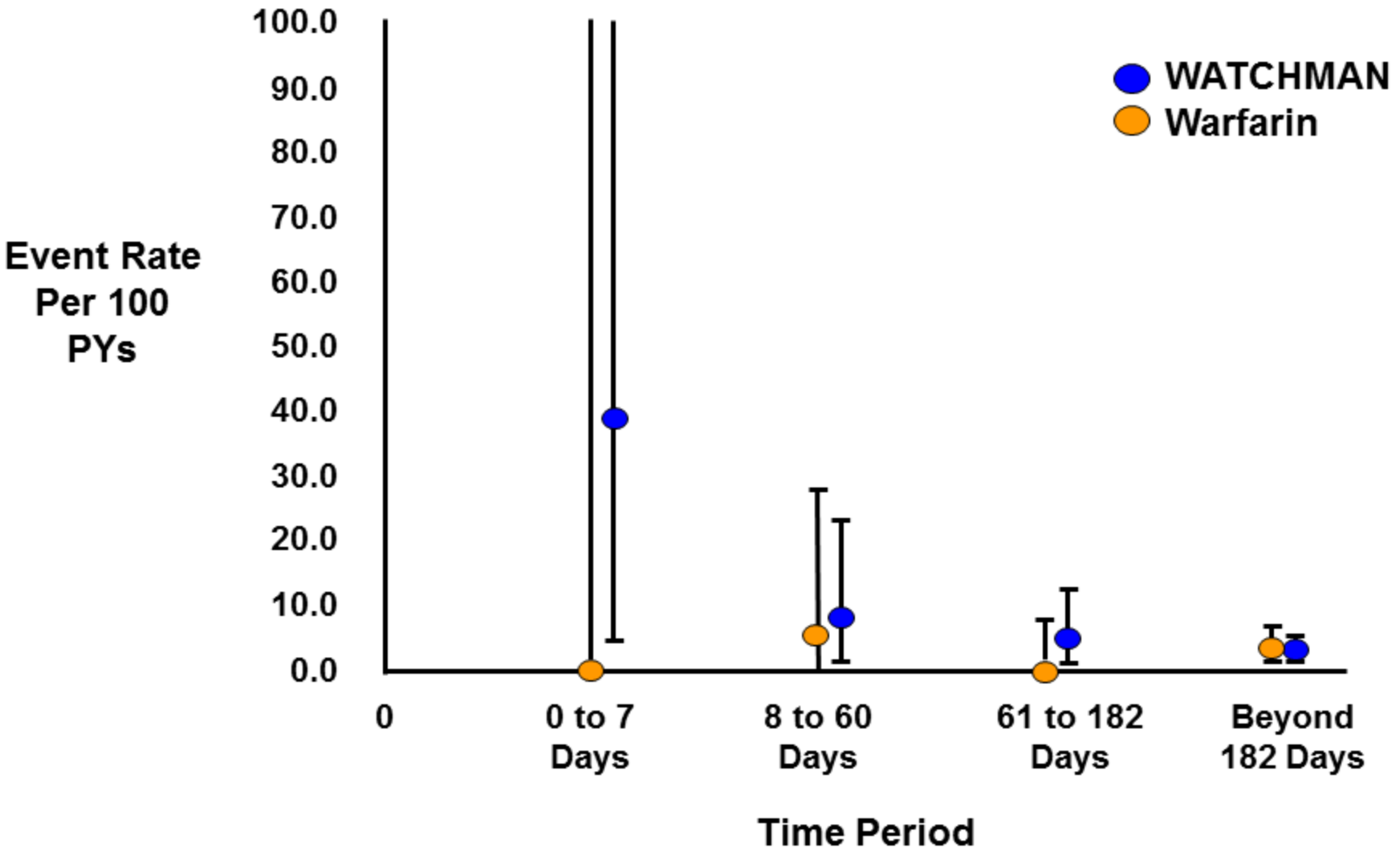
Hemorrhagic Stroke
(includes fatal and non-fatal events)

Free of Ischemic Stroke



N=1000; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years;
*Friberg. Eur Heart J (2012)

PREVAIL CSR Figure 12-3: Event Rates by Piecewise Intervals (PREVAIL-only)



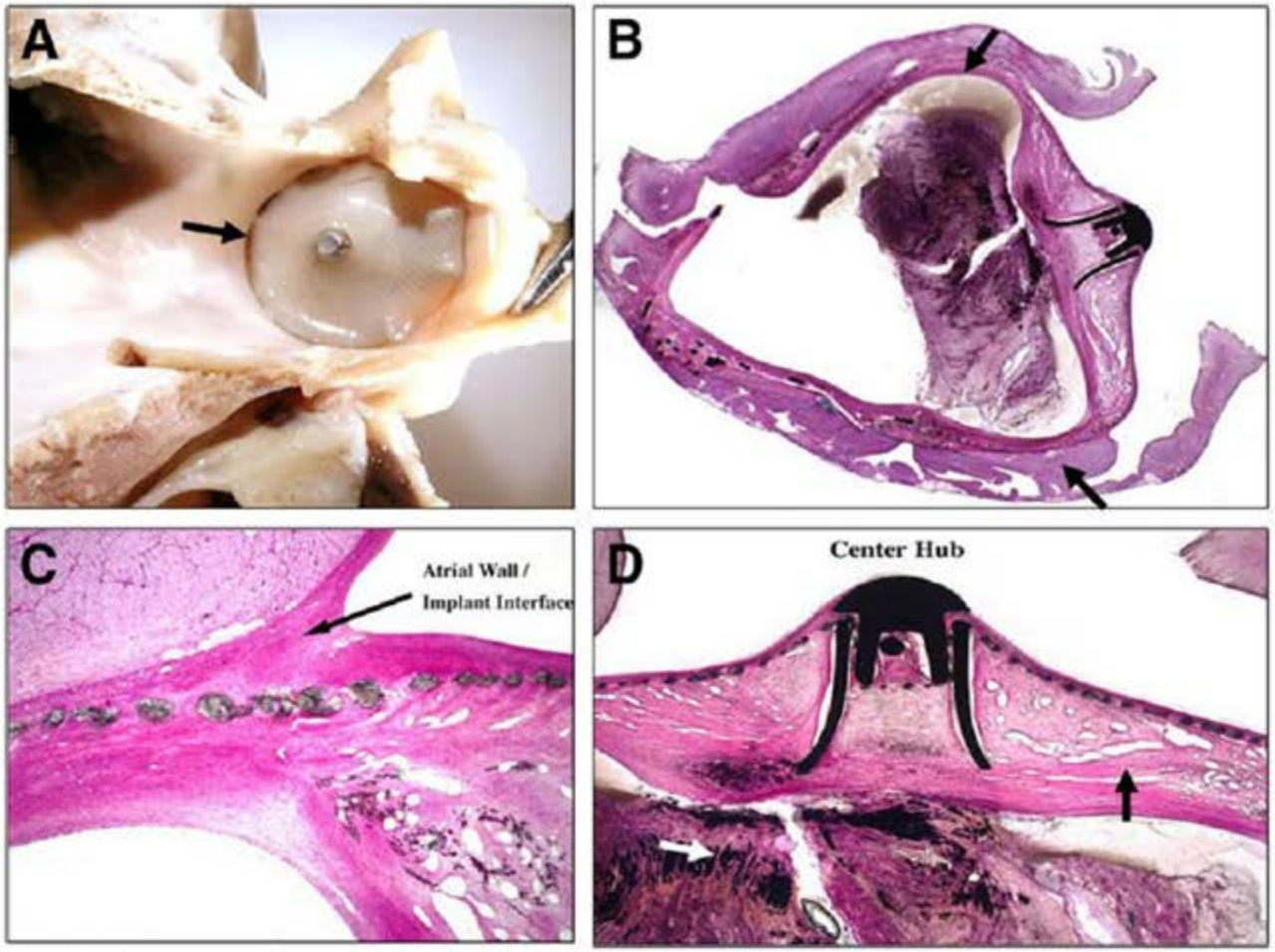
Endothelialization

- Canine model[1]:
  - Endothelial cell lining by 45 days
  - Complete endocardial lining by 90 days without residual inflammation
  - More recent data: all surfaces completely incorporated with organizing endocardial growth at 28 days[2]
- Human autopsy series[1]:
  - 139, 200, 480, and 852 days after implant
  - ostial fabric membrane covered with endocardium

1. J Am Coll Cardiol Intv (2010)
2. EuroPCR Abstract Friday May 24th 2013

Device Endothelialization

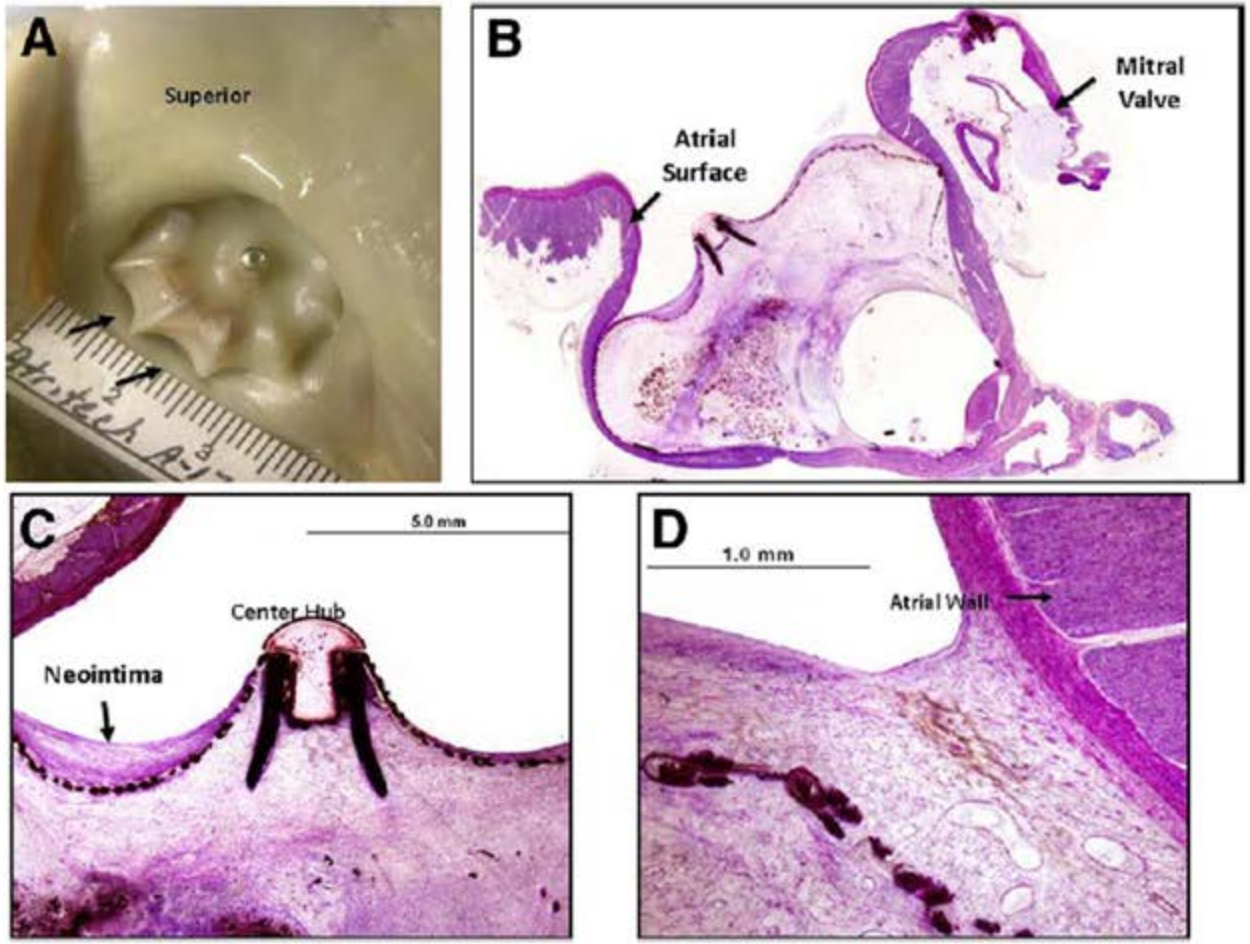
Dog Heart, 45 days After WATCHMAN Implantation



J Am Coll Cardiol Intv 2010;3:870–7

Device Endothelialization

Human Heart, 200 days After WATCHMAN Implantation



J Am Coll Cardiol Intv 2010;3:870–7

CEC Adjudication of Stroke Type Hemorrhagic Event Definitions

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